Synthesis of Cyclic Acylated Enamino Esters from Enol Lactones, 4-Keto Amides, and 5-Hydroxy Lactams

A. D. Abell,* M. D. Oldham, and J. M. Taylor

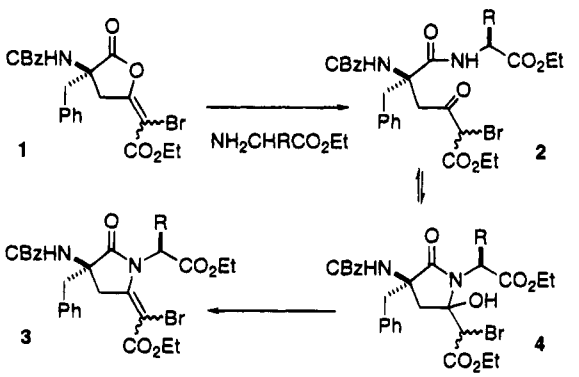
Department of Chemistry, University of Canterbury, Christchurch, New Zealand

Received July 19, 1994 (Revised Manuscript Received October 26, 1994®)

Enol lactones react with an amine to give either a keto amide or a hydroxy lactam under mild conditions. Subsequent dehydration with *p*-toluenesulfonic acid (PTSA) gives a cyclic acylated enamino ester in good yield (Tables 1 and 2, Schemes 2 and 4). The key prostaglandin analog precursor **18** and the gly-gly dipeptide analogs **26a** and **26b** were prepared using the reported conditions. Acetylation of the chloro hydroxy lactam **31**, prepared from the chloro enol lactones **29**, followed by elimination of acetic acid gave the chloro acylated enamino esters **28**.

Examples of cyclic acylated enamino esters, and related compounds have been reported as peptide mimics[1] **3**, Angiotensin II antagonists,[2] and synthetic precursors to γ-lactam antibiotics,[3] tetrapyrrolic pigments,[4–6] prostaglandin analogues **18**,[7] and other natural products.[8] Acylated enamino esters are traditionally prepared from the corresponding imide via either a Wittig, Reformatsky, or Grignard reaction.[9–11] These reactions suffer from low yields, harsh reaction conditions, and undesirable side reactions. Cyclic acylated enamino esters have also been prepared from the reactions of a dimethyl β-oxoalkanedioate with an amine,[3,12] an oxirane with sodium azide and ammonium chloride,[13] and other methods.[7] These methods also give at best modest yields and lack generality. In this paper, we report a study on the reaction of an enol lactone, e.g., **5**, and an amine, e.g., an amino acid, as a general and convenient synthesis of cyclic acylated enamino esters, e.g., compound **15** (Table 2). Isolated reports on this general reaction have appeared in the literature[1,2] including our preliminary communication[1] on the preparation of peptide mmics of the type **3** as shown in Scheme 1. We now show that the isolation of a reaction intermediate in this general reaction (Table 1, compounds of the type **6** or **7**) and its subsequent dehydration is the method of choice for the preparation of the cyclic acylated enamino esters. The precusor enol lactones are readily prepared in high yields from the reaction of an anhydride and a stabilized ylide.[1,11] As stated earlier, the analogous Wittig reaction

Scheme 1



of an imide requires harsh reaction conditions and gives low yields of the corresponding cyclic acylated enamino ester.[9–11]

Results and Discussion

An extended reaction of the enol lactone **5a** with either methylamine, ethylamine or butylamine gave the (*E*)-acylated enamino esters **8a–c** in 69–100% yield (Table 1, entries 1–3). A similar reaction of the enol lactones **5b** (Table 1, entry 6) or **9** (Scheme 2) with butylamine gave a poor yield of the corresponding acylated enamino esters **8e,f** and **11a,b**, respectively. One equiv of pyridine has been used to facilitate reactions of this type;[2] however, we found that the best yields of **8e,f** and **11a,b** were obtained by first isolating the keto amide **6a** (Table 1, entry 7) and the hydroxy lactam **12a** (Scheme 2), respectively, under mild conditions. *p*-Toluenesulfonic acid (PTSA) catalyzed azeotropic removal of water from **6a** and **12a** then gave (*E*)- and (*Z*)-mixtures of the acylated enamino esters **8f,g** (Table 1, entry 8) and **11a,b** (Scheme 2), respectively.

The two-step procedure reported here gave high yields of acylated enamino esters derived from a range of amines and enol lactones. For example, the reaction of enol lactone **5a** and an amino acid ester gave the keto amides **13a–d** (Table 2). The cyclic acylated enamino esters **15**, simple analogs of the peptide mimics **3**, were then obtained in high yields by PTSA-catalyzed cyclization and dehydration of **13** (Table 2). The glycine-derived keto amide **13a** underwent dehydration much more readily than the alanine-, leucine-, and phenylalanine-derived **13b–d** (Table 2). The enol lactone **9** also reacted with glycine ethyl ester via a two-step sequence to give

® Abstract published in *Advance ACS Abstracts,* February 15, 1995.

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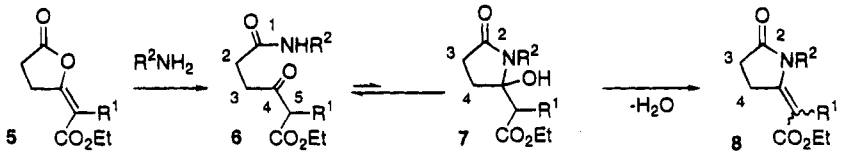
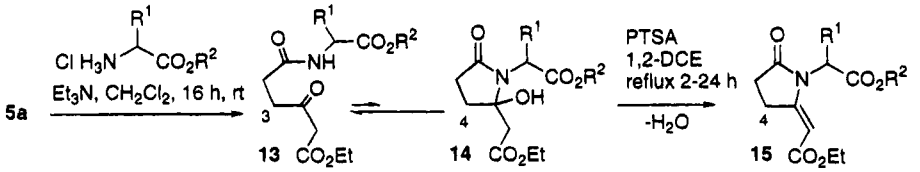
Table 1



entry	starting material	R^1	condns[a]	R^2	product	yield (%)
1	**5a**	H	a	Me	(*E*)-**8a**	93
2			a	Et	(*E*)-**8b**	69
3			a	Bu	(*E*)-**8c**	100
4			b	H	7a	100
5	**7a**	H	c	H	(*Z*)-**8d**	83
6	**5b**	Me	a	Bu	(*E*)-**8e**, (*Z*)-**8f**	20
7			d	Bu	6a	100
8	**6a**	Me	e	Bu	(*E*)-**8e**, (*Z*)-**8f**	69

[a] Conditions: (a) R^2NH_2, 4 Å sieves, 1,2-DCE, 65 °C, 3–4 days; (b) NH_3, EtOH, 5 h, rt; (c) 4 Å sieves, 65 °C, 1,2-DCE, 72 h; (d) R^2NH_2, CH_2Cl_2 or 1,2-DCE, rt, 16 h; (e) PTSA, 1,2-DCE, reflux, 10 h.

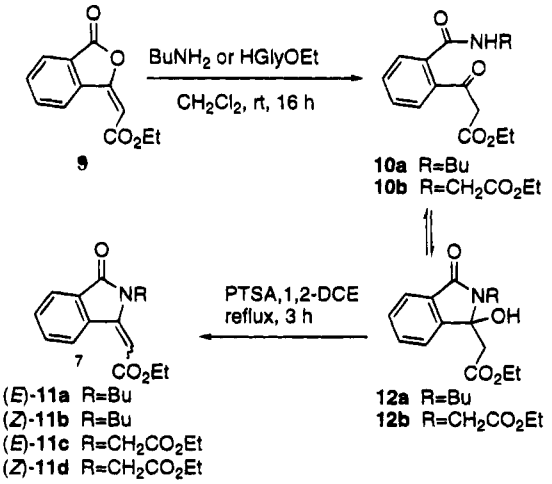
Table 2



R^1	keto amide	R^2	yield (%)	product	R^2	yield (%)	time (h)
H	**13a**	Et	88	**15a**	Et	83	2[a]
Me	**13b**	Et	73	**15b**	Et	84	24
$CH_2CH(Me)_2$	**13c**	Et	quant	**15c**	Et	84	20
CH_2Ph	**13d**	Et	97	**15d**	Et	86	24

[a] Reaction carried out in benzene.

Scheme 2



11c and **11d** (Scheme 2). Here, the hydroxy lactam **12b**, rather than the keto amide **10b**, was isolated after step 1 (Scheme 2). The isolation of the hydroxy lactams **12a** and **12b** from the reaction of the aromatic enol lactone **9** with butylamine and glycine ethyl ester, respectively, reflects the propensity of **10a** and **10b**, the likely precursors to **12a** and **12b**, toward cyclization. The ease of cyclization of the keto amides **10a** and **10b** contrasts other reports of hydroxy lactam formation.[14]

The reaction of **5a** with a large excess of ammonia in ethanol gave the hydroxy lactam **7a**, rather than the alternative keto amide, (Table 1, entry 4). Subsequent reaction at 65 °C gave the (*Z*)-acylated enamino ester **8d** in 83% yield (Table 1, entry 5). For comparison, **8d** was obtained via the oxirane, Wittig, and Reformatsky routes in 67%,[13] 32%,[10] and 21% yields,[10] respectively. The methyl ester equivalent of **8d** has also been prepared in 56% yield from dimethyl 3-oxohexanedioate.[12] The apparent stability of the hydroxy lactam **7a** may be due to intramolecular hydrogen bonding between the CO_2Et and N*H* groups.

The ^1H NMR and ^{13}C NMR spectra of the keto amides and hydroxy lactams were consistent with the assigned structures. The $(H2)_2$ and $(H3)_2$ resonances of the achiral keto amide **13a** appeared as a triplet. However, the resonances for the diastereotopic $(H3)_2$ protons of the keto amide **6a** and the amino acid derived keto amides **13b–d** appeared as multiplets (for an atom numbering scheme see Table 1). The alternative hydroxy lactam structures, e.g., **4**[1] and **14**, would be expected to exist as a mixture of stereoisomers. The most characteristic resonances in the ^{13}C NMR spectra of the hydroxy lactams **7a**, **12a**, and **12b** were those arising from *C*OH at δ 88.3, 87.9, and 86.4, respectively.

An application of the reported reaction sequence was demonstrated with the synthesis of compound **18** (Scheme 3), a key synthetic intermediate to prostaglandin analogs.[7] Reaction of the enol lactone **16** with methyl 7-aminoheptanoate gave a mixture of the keto amide **17** and the corresponding enol form **19** in a ratio of 1:4 (by ^1H NMR spectroscopy). The mixture was refluxed in 1,2-DCE containing PTSA to give compound **18** in an overall yield of 75%. Compound **18** was assigned the (*E*)-

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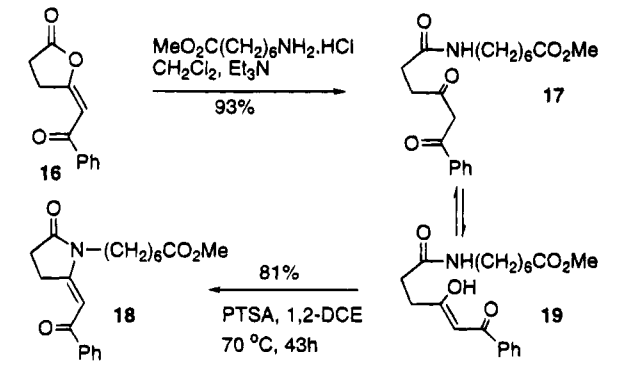
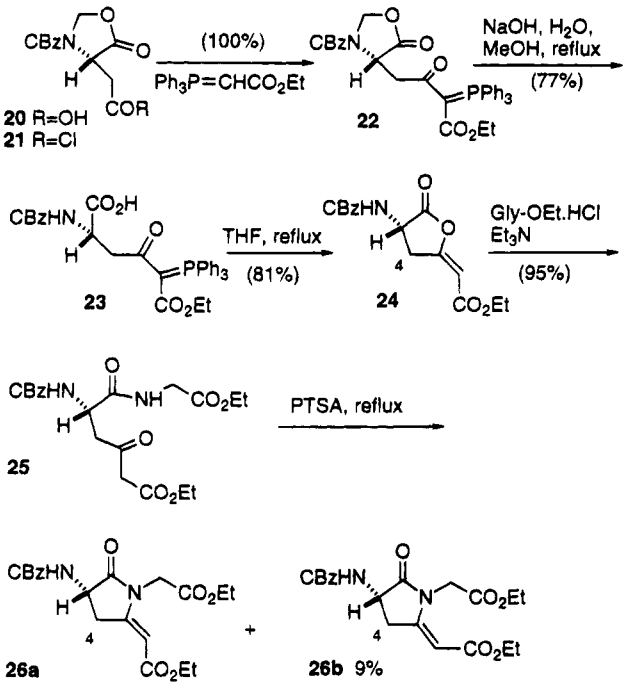
Scheme 3



Scheme 4



configuration, in contrast to the previous report,[7] on the basis of a 3.44 ppm chemical shift for $(H4)_2$ (see the following text for a discussion). The literature five-step synthesis of compound **18** gave a yield of 50%.[7]

The gly-gly dipeptide mimics **26a** and **26b**, further examples of a new class of peptide mimic,[1] were also prepared by this methodology. The reaction of *N*-CBz-L-aspartic acid with p-formaldehyde and PTSA according to the method of Scholtz and Bartlett[15] gave the oxazolidinone acid **20**. (The stereochemical integrity of **20** was confirmed by a dicyclohexylcarbodiimide (DCC) catalyzed coupling of **20** with (*R*)-(+)-1-(1-naphthyl)ethylamine to give the corresponding amide as a single diastereoisomer by ^{1}H NMR spectroscopy.) Reaction with oxalyl chloride and DMF then gave a quantitative yield of the acid chloride **21** (Scheme 4). The reaction of the acid chloride **21** with 2 equiv of Ph_3PCHCO_2Et gave the keto acid phosphorane **22** (Scheme 4). Compound **22** gave a characteristic[16] ^{13}C NMR spectrum with $^{13}C-^{31}P$ coupling constants (Hz) of 109.7 (C=PPh_3), 93.7 (C1 of PPh_3), 12.1 (*m*-C of PPh_3), 3.0 (*p*-C of PPh_3), 10.0 (*ortho*-C of PPh_3), 5.1 (CO_2Et), and 5.0 (ketone). The oxazolidinone ring of **22** was hydrolyzed to give the free acid **23** which was heated in THF to give the key intermediate (*E*)-enol lactone **24**.

The reaction of the enol lactone **24** with glycine ethyl ester gave the keto amide **25** (Scheme 4). PTSA-catalyzed removal of water then gave the enamino esters **26a** and **26b**. A possible alternative, and potentially direct, preparation of the enol lactone **24** involving the reaction of *N*-CBz-L-aspartic anhydride with Ph_3PCHCO_2-Et gave the undesired regioisomer as the only isolated product. Stabilized ylides are known to react at either the 2 or 5 positions of a substituted succinic anhydride depending on the nature of the substitution.[17] The cyclization of a keto acid phosphorane of the type **23** generally gives the (*E*)-enol lactone rather the (*Z*)-enol lactone.[17] This observation, together with the downfield position[17,18] of the $(H4)_2$ resonances at δ 3.25 (dd) and 3.89 (dd), was used to assign the (*E*)-configuration to **24**. The $(H4)_2$ resonances for the (*E*)-enamino ester **26a** were also in characteristic and well-separated downfield positions (δ 3.11, dd and 3.91, dd) relative to the (*Z*)-isomer **26b** (δ 2.60, m). The downfield shift of the $(H4)_2$ resonances in the (*E*)-configuration is a result of the deshielding influence of the vinyl ester group.[17] The ^{1}H NMR spectra of **26a** and **24**, both assigned the (*E*)-configuration, were very simlar in all respects.

Similar chemical shifts for the $(H4)_2$ resonances of **8a–c,e** (Table 1) and **15** (Table 2) were consistent with the assigned (*E*)-configurations. The assignment of the (*E*)-configuration to the major isomer **8e** was also consistent with an observed NOE between the NCH_2 and vinyl methyl groups. The minor (*Z*)-isomer **8f** gave a characteristic NOE between $(H4)_2$ and the vinyl methyl groups (see Table 1 for atom numbering). Similarly, the H7 resonance for **11** is characteristically deshielded in the (*E*)-isomer relative to the (*Z*)-isomer.[10] The (*Z*)-configuration of **8d** was readily assigned on the basis of the upfield position of the vinyl proton.[13] The NH resonance of the (*Z*)-isomer of **8d** is also characteristically downfield relative to the (*E*)-isomer as a result of intramolecular hydrogen bonding to the CO_2Et group.[13]

Finally, the reaction of the chloro enol lactones **29**, glycine ethyl ester hydrochloride, and triethylamine in ethyl acetate (Scheme 5) gave a mixture containing the keto amide **30** and the hydroxy lactam **31** in a ratio of 3:1 by ^{1}H NMR spectroscopy. The chloro keto amide **30** formed more readily than the corresponding protio and methyl keto amides (compare the reactions given in Tables 1 and 2). Dehydration of the mixture of **30** and **31** with PTSA gave the imide **27** (57%) and a low yield of the desired (*E*)- and (*Z*)-chloro acylated enamino esters **28** (13% of each isomer) (Scheme 5, pathway A). Formation of the imide **27** was effectively blocked by acetylating the mixture of **30** and **31** to give **33** (Scheme 5, pathway B). Heating the acetates **33** in benzene gave **32** (15%) and the (*E*)- and (*Z*)-enamino esters **28** (44% *E*:56% *Z* by ^{1}H NMR spectroscopy) in a much improved yield of 78%. The (*E*)- and (*Z*)-chloro enamino esters **28** proved unstable and eliminated HCl on standing or distillation to give the (*E*)- and (*Z*)-isomers of **32**. The configuration of the (*Z*)-isomer **28b** was assigned on the basis of a

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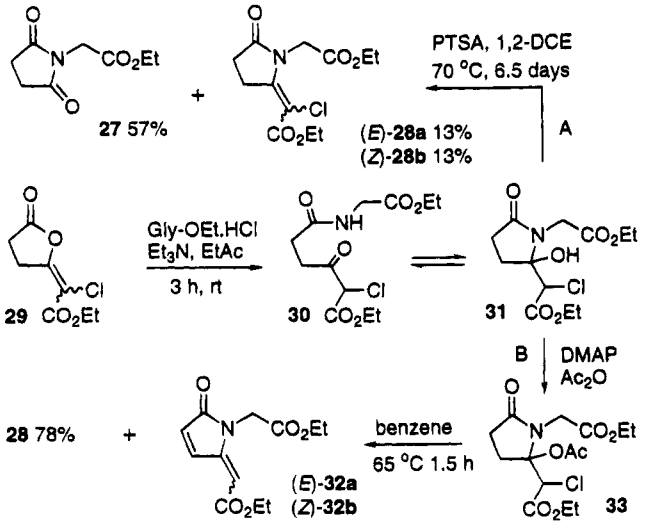
Scheme 5



downfield shift of 0.35 ppm for $(H4)_2$ relative to the (*E*)-isomer **28a**. The assignment was supported by the ^1H NMR assignments of the (*E*)- and (*Z*)-chloro enol lactones **29**.[18]

In conclusion, a convenient preparation of acylated succinamide- and phthalimide-based acylated enamino esters from readily available enol lactones is reported. The reactions are easily carried out and high yielding and in addition should be applicable to the many and varied classes of known enol lactones.[11]

Experimental Section

General Methods. All solvents and the amines were freshly distilled prior to use. The enol lactones **5a**,[19] **5b**,[17b] **9**,[19] **16**,[19] and **35**[18] were prepared by previously described methods. Solutions of ammonia in EtOH were prepared by bubbling ammonia into preweighed and ice-cooled EtOH. Melting points were taken using a Reichert hot-stage microscope and are uncorrected. Infrared spectra were recorded on either a Pye Unicam SP3−300 or Perkin-Elmer 1600 Series FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian CFT300 spectrometer in $CDCl_3$ solutions with Me_4Si as an internal standard. Mass spectra were obtained using a Kratos MS80RFA spectrometer. Radial chromatography was performed on a chromatotron (Harrison and Harrison) using Merk type 60 P. F_{254} silica gel. Petroleum ether refers to the fraction of bp 60−70 °.

General Method for the Preparation of the Keto Amides 6a and the Hydroxy Lactam 12a. The amine (typically 1.8 equiv) was added to the appropriate enol lactone (typically 0.12 mmol) dissolved in CH_2Cl_2 or 1,2-dichloroethane (5 mL), and the solution was stirred for 16 h at 20 °C. The solvent was evaporated at 20 mm and finally at 1 mm to yield the product, which was used in subsequent steps without further purification.

(a) (±)-*N*-Butyl-5-(ethoxycarbonyl)-5-methyl-4-oxopentamide (6a). The enol lactone **5b** and butylamine in CH_2Cl_2 gave **6a**, quant: IR (film) 3325, 1750, 1725, 1660, 1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.32 (m, 2H), 1.35 (d, *J* = 7.2 Hz, 3H), 1.47 (m, 2H), 2.45 (m, $(H3)_2$), 2.91 (t, *J* = 6.5 Hz, $(H2)_2$), 3.22 (m, 2H), 3.58 (q, *J* = 7.2 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 5.75 (brs, NH); ^{13}C NMR ($CDCl_3$) δ 12.72, 13.67, 14.03, 19.98, 29.96, 31.59, 36.71, 39.32, 52.74, 61.37, 170.47, 171.38, 205.28; HRMS calcd for $C_{13}H_{23}NO_4$ 257.1628, found 257.1620.

(b) (±)-2-Butyl-3-[(ethoxycarbonyl)methyl]-3-hydroxyisoindolone (12a). Enol lactone **9** and butylamine in CH_2Cl_2 gave **12a**, quant: IR (KBr) 3350, 1750, 1680, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.3 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H), 1.36 (sextet, *J* = 7.4 Hz, 2H), 1.62 (m, 2H), 2.99 and 3.13 (AB_q), 3.20 (m, 1H), 3.51 (m, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 7.44 (m, 1H), 7.53 (m, 2H), 7.65 (dt, *J* = 1.0, 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.76, 13.84, 20.57, 31.17, 38.96, 41.50, 61.13, 88.33, 121.72, 123.15, 129.66, 131.13 132.11, 146.32, 167.28, 169.78; HRMS calcd for $C_{16}H_{21}NO_4$ 291.1471, found 291.1473.

(±)-5-[(Ethoxycarbonyl)methyl]-5-hydroxy-2-pyrrolidinone (7a). Ammonia (0.7 mL of 22.5 mg/mL solution in ethanol, 0.9 mmol) was added to enol lactone **5a** (15 mg, 0.09 mmol) in CH_2Cl_2 (3 mL) and the solution was stirred at 20 °C for 5 h. The solvent was evaporated to give **7a** (quant) as an oil, which was used in subsequent steps without further purification: IR (film) 3400, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, *J* = 7.2 Hz, 3H), 2.11 (m, 1H), 2.28 (m, 1H), 2.34 (m, 1H), 2.60 (m, 1H), 2.75 and 2.93 (AB_q, *J* = 17.0 Hz), 4.23 (q, *J* = 7.2 Hz, 2H), 6.60 (brs, NH); ^{13}C NMR ($CDCl_3$) δ 13.93, 29.19, 34.60, 45.09, 60.95, 86.36, 170.55, 177.82; HRMS calcd for $C_8H_{13}NO_4$ 187.0845, found 187.0848.

General Method for the Preparation of the Amino Acid-Derived Keto Amides 13 and Hydroxy Lactam 12b. The amino acid ester hydrochloride (typically 1.3 equiv) and triethylamine (1.3 equiv) were added to the enol lactone (typically 0.47 mmol) dissolved in CH_2Cl_2 (8 mL), and the mixture was stirred for 16 h at 20 °C, during which time homogeneity was achieved. The solution was washed with water (10 mL) and dried ($MgSO_4$) and the solvent evaporated at 20 mm and finally at 1 mm to yield the product, which was used in subsequent steps without further purification.

(a) 5-(Ethoxycarbonyl)-*N*-[(ethoxycarbonyl)methyl]-4-oxopentamide (13a). The enol lactone **5a** and glycine ethyl ester hydrochloride gave **13a**, 88%: mp 66.5−68.5 °C (ethyl acetate/petroleum ether, white crystals); IR (KBr) 3325, 1760, 1720, 1660, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 2.56 (t, *J* = 6.5 Hz, $(H3)_2$), 2.92 (t, *J* = 6.5 Hz, $(H2)_2$), 3.50 (s, $(H5)_2$), 4.01 (d, *J* = 5.2 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 6.11 (brs, NH); ^{13}C NMR ($CDCl_3$) δ 13.94, 13.99, 29.27, 37.69, 41.32, 49.07, 61.26, 61.30, 166.99, 169.80, 171.60, 201.80. Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.59; H, 7.01; N, 5.01.

(b) (±)-5-(Ethoxycarbonyl)-*N*-[1-(ethoxycarbonyl)ethyl]-4-oxopentamide (13b). The enol lactone **5a** and D,L-alanine ethyl ester hydrochloride gave **13b**, 73%: IR (KBr) 3325, 1760, 1720, 1650, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.39 (d, *J* = 7.2 Hz, 3H), 2.53 (t, *J* = 6.5 Hz, $(H3)_2$), 2.91 (m, $(H2)_2$), 3.50 (s, $(H5)_2$), 4.20 (q, *J* = 7.2 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, OCH_2), 4.53 (m, 3H), 6.15 (bd, *J* = 6.8 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 14.09, 14.11, 18.46, 29.65, 37.78, 48.23, 49.26, 61.42, 61.50, 167.07, 170.86, 173.01, 201.77; HRMS calcd for $C_{13}H_{21}NO_6$ 287.1369, found 287.1376.

(c) (±)-5-(Ethoxycarbonyl)-*N*-[1-(ethoxycarbonyl)-3-methylbutyl]-4-oxo-pentamide (13c). The enol lactone **5a** and D,L-leucine ethyl ester hydrochloride gave **13c**, quant: IR (film) 3350, 1750, 1660, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, *J* = 1.5 Hz, 3H), 0.95 (d, *J* = 1.5 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.60 (m, 3H), 2.53 (t, *J* = 6.3 Hz $(H3)_2$), 2.91 (m, $(H2)_2$), 3.49 (s, $(H5)_2$), 4.18 (q, *J* = 7.1 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.58 (m, 1H), 5.96 (bd, *J* = 7.6 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 14.05, 14.09, 21.97, 22.72, 24.80, 29.61, 37.81, 41.65, 49.19, 50.86, 61.27, 61.37, 167.05, 171.12, 172.99, 201.70; HRMS calcd for $C_{16}H_{27}NO_6$ 329.1839, found 329.1837.

(d) (±)-5-(Ethoxycarbonyl)-*N*-[1-(ethoxycarbonyl)-2-phenylethyl]-4-oxo-pentamide (13d). The enol lactone **5a** and D,L-phenylalanine ethyl ester hydrochloride gave **13d**, 97%: IR (KBr) 3340, 1740, 1720, 1655, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 2.49 (dt, *J* = 1.7, 6.6 Hz, $(H3)_2$), 2.88 (m, $(H2)_2$), 3.11 (dd, *J* = 2.2, 5.8 Hz, 2H), 3.48 (s, $(H5)_2$), 4.17 (q, *J* = 7.1 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.82 (m, 1H), 6.03 (bd, *J* = 7.2 Hz, NH), 7.12 (m, 2H), 7.27 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.05, 14.05, 29.55, 37.66, 37.89, 49.19, 53.21, 61.36, 61.44, 127.02, 128.46,

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

129.33, 135.84, 167.03, 170.84, 171.41, 201.58; HRMS calcd for $C_{19}H_{25}NO_6$ 363.1683, found 363.1681.

(e) (±)-2,3-Bis[(ethoxycarbonyl)methyl]-3-hydroxyisoindolone (12b). The enol lactone **9** and glycine ethyl ester hydrochloride gave **12b**, 79%: IR (film) 3400, 1750, 1720, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 3.07 and 3.14 (AB_q, J = 15.3 Hz), 4.00 (q, J = 7.2 Hz, 2H), 4.16 and 4.53 (AB_q, J = 17.9 Hz), 4.23 (q, J = 7.1 Hz, 2H), 7.52 (m, 1H), 7.62 (m, 2H), 7.81 (dt, J = 1.0, 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.71, 13.98, 40.35, 41.78, 60.86, 61.66, 87.92, 122.13, 123.37, 129.71, 130.14, 132.59, 146.55, 167.22, 168.84, 170.19; HRMS calcd for $C_{16}H_{19}NO_6$ 321.1213, found 321.1208.

General Methods for the Preparation of Enamino Esters 8, 11, and 15: Method A. The appropriate keto amide or hydroxy lactam (stated amount, 1 equiv) and a catalytic amount of PTSA, dissolved in 1,2-dichloroethane, were refluxed with azeotropic removal of H_2O for the indicated time. The solution was cooled to 20 °C, washed with H_2O (15 mL), and dried ($MgSO_4$) and the solvent evaporated to yield the enamino ester. **Method B.** As for general method A except that the solvent used was benzene. **Method C.** The enol lactone or keto amide (stated amount) and the indicated amine (stated amount) were dissolved in 1,2-dichloroethane. Activated 4 Å molecular sieves were added, and the solution was stirred at 65 °C for 3 days and filtered, and the solvent was evaporated to yield the enamino ester.

(a) (*E*)-1-Methyl-5-[(ethoxycarbonyl)methylidene]-2-pyrrolidinone[13] (8a). General method C with enol lactone **5a** (20 mg, 0.12 mmol) and methylamine (52 μL of 3.91 M solution in 1,2-dichloroethane, 0.20 mmol, 1.7 equiv) in 1,2-dichloroethane (5 mL) gave **8a**,[13] 93%.

(b) (*E*)-1-Ethyl-5-[(ethoxycarbonyl)methylidene]-2-pyrrolidinone (8b). General method B with keto amide **6b** (67 mg, 0.29 mmol) and a catalytic quantity of PTSA in benzene (15 mL), and a reflux time of 3 h gave **8b**, 71%: mp 158–159 °C; IR (KBr) 1745, 1715, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 2.55 (m, $(H3)_2$), 3.23 (m, $(H4)_2$), 3.58 (q, J = 7.2 Hz, NCH_2), 4.17 (q, J = 7.1 Hz, 2H), 5.23 (t, J = 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.63, 14.39, 24.68, 27.98, 35.23, 59.48, 91.21, 159.50, 167.33, 176.61. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.65; H, 7.77; N, 6.63. General method C with enol lactone **5a** (50 mg, 0.29 mmol) and ethylamine (0.25 μL, 0.38 mmol, 1.3 equiv) in 1,2-dichloroethane (10 mL) gave **8b**, 69%.

(c) (*E*)-1-Butyl 5-[(ethoxycarbonyl)methylidene]-2-pyrrolidinone (8c). General method C with enol lactone **5a** (50 mg, 0.29 mmol) and butylamine (39 μL, 0.38 mmol, 1.3 equiv) in 1,2-dichloroethane (10 mL) gave **8c**, 100%: bp 175 °C (1 mm); IR (film) 1750, 1715, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.32 (m, 2H), 1.54 (m, 2H), 2.55 (m, $(H3)_2$), 3.23 (m, $(H4)_2$), 3.51 (t, J = 7.6 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H), 5.21 (t, J = 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.56, 14.33, 20.06, 24.62, 27.84, 28.30, 40.23, 59.40, 91.22, 159.83, 167.26, 176.79. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.73; H, 8.36; N, 6.37.

(d) (*Z*)-5-[(Ethoxycarbonyl)methylidene]-2-pyrrolidinone[10] (8d). General method C with hydroxy lactam **7a** (12 mg, 0.064 mmol) in 1,2-dichloroethane (5 mL) gave **8d**, 83%: mp 79–81 °C (ethanol/H_2O) (lit.[10] mp 81–81 °C).

(e) (*E*)- and (*Z*)-1-Butyl-5-[1-(ethoxycarbonyl)ethylidene]-2-pyrrolidinone (8e) and (8f). General method A with keto amide **6a** (112 mg, 0.44 mmol) and a catalytic quantity of PTSA, in 1,2-dichloroethane (15 mL), and a reflux time of 10 h gave a mixture containing (*E*)- and (*Z*)-enamino esters (**8e** and **8f**, respectively) in the ratio of 84% *E*:16% *Z*, by ^1H NMR. Purification by radial chromatography eluting with 75% petroleum ether/25% ethyl acetate gave (*E*)-enamino ester **8e**, 60%: IR (film) 1740, 1710, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.31 (m, 2H), 1.55 (m, 2H), 2.06 (t, J = 1.2 Hz, 3H), 2.47 (m, $(H3)_2$), 3.13 (m, $(H4)_2$), 3.78 (t, J = 7.7 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.48, 13.70, 14.35, 19.84, 27.96, 28.68, 30.76, 42.63, 60.17, 101.44, 153.11, 169.25, 178.56; HRMS calcd for $C_{13}H_{21}NO_3$ 239.1522, found 239.1521. Further elution gave a fraction containing the (*Z*)-enamino ester **8f** and the (*E*)-isomer **8e** (9%, 82:18 by ^1H NMR): IR (film) 1740, 1710, 1630 cm^{-1}; ^1H NMR **8f** ($CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.23 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H), 1.35 (m, 2H), 1.91 (t, J = 1.1 Hz, 3H), 2.51 (m, $(H3)_2$), 2.64 (m, $(H4)_2$), 3.73 (t, J = 7.5 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.76, 14.26, 16.46, 19.94, 25.36, 28.13, 28.49, 41.47, 60.68, 101.23, 143.84, 168.73, 177.40; HRMS calcd for $C_{13}H_{21}NO_3$ 239.1522, found 239.1524.

(f) (*E*)- and (*Z*)-2-Butyl 3-[(ethoxycarbonyl)methylidene]isoindolone (11a) and (11b). General method A with hydroxy lactam **12a** (150 mg, 0.51 mmol) and a catalytic quantity of PTSA, in 1,2-dichloroethane (15 mL), and a reflux time of 3 h gave a mixture, 76%, of (*E*)- and (*Z*)-enamino esters (**11a** and **11b**, respectively) (86% *E*:14% *Z*, by ^1H NMR). The (*E*)-isomer **11a** was isolated by crystallization (ethanol/H_2O): mp 72–73 °C; IR (KBr) 1725, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H), 1.39 (m, 2H), 1.65 (m, 2H), 3.79 (t, J = 7.4 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 5.71 (s, 1H), 7.57 (dt, J = 1.1, 7.4 Hz, H4), 7.65 (dt, J = 1.4, 7.6 Hz, H5), 7.85 (dd, J = 0.9, 6.3 Hz, H3), 9.06 (d, J = 7.8 Hz, H4); ^{13}C NMR ($CDCl_3$) δ 13.60, 14.23, 20.01, 29.77, 39.18, 60.34, 98.21, 122.85, 127.82, 129.92, 130.95, 132.85, 133.66, 148.04, 165.88, 167.07. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.26; H, 7.18; N, 5.17. (*Z*)-Isomer **11b** (from mixture): ^1H NMR ($CDCl_3$) δ 5.88 (s, =CH); ^{13}C NMR ($CDCl_3$) δ 13.76, 19.71, 30.93, 41.84, 60.44, 93.84, 119.77, 123.38, 128.10, 130.59, 132.31, 137.75, 143.86, 164.71, 168.56.

(g) (*E*)- and (*Z*)-2-[(Ethoxycarbonyl)methyl]-3-[(ethoxycarbonyl)methylidene]isoindolone (11c) and (11d). General method A with hydroxy lactam **12b** (134 mg, 0.42 mmol) and a catalytic quantity of PTSA, in 1,2-dichloroethane (15 mL), and a reflux time of 3 h gave a mixture of (*E*)- and (*Z*)-enamino esters (**11c** and **11d**, respectively) (60% *E*:40% *Z*, by ^1H NMR), 90%. On recrystallization (ethanol/H_2O) the isomer ratio changed to 45% *E*:55% *Z* by ^1H NMR: IR (KBr) 1750, 1730, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) (*E*)-isomer **11c** from mixture δ 1.29 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 4.25 (q, J = 7.1 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 4.56 (s, 2H), 5.54 (s, 1H), 7.61 (dt, J = 1.1, 7.4 Hz, H6), 7.70 (dt, J = 1.4, 7.7 Hz, H5), 7.89 (dd, J = 0.9, 6.7 Hz, H7), 9.10 (d, J = 7.8 Hz, H4); (*Z*)-isomer **11d** from mixture δ 1.28 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 4.19 (q, J = 7.1 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 5.15 (s, 2H), 5.92 (s, 1H), 7.56–7.73 and 7.86–7.89 (m, 4H, H4, H5, H6 and H7); ^{13}C NMR ($CDCl_3$) (*E*)-isomer **11c** from mixture δ 13.97, 14.16, 41.00, 60.44, 61.75, 98.68, 123.27, 128.14, 129.44, 131.21, 133.35, 133.74, 147.71, 165.45, 167.16, 168.74; (*Z*)-isomer **11d** from mixture δ 14.05, 14.08, 44.39, 60.21, 61.11, 94.56, 120.14, 123.76, 127.43, 130.90, 132.84, 137.72, 144.44, 164.83, 166.73, 168.23. Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.36; H, 5.65; N, 4.74.

(h) (*E*)-1-[(Ethoxycarbonyl)methyl]-5-[(ethoxycarbonyl)methylidene]-2-pyrrolidinone (15a). General method B with keto amide **13a** (40 mg, 0.15 mmol) and a catalytic quantity of PTSA, in benzene (15 mL), and a reflux time of 2 h gave **15a**, 83%: mp 111–112 °C (ethyl acetate/petroleum ether, colorless crystals); IR (KBr) 1760, 1720, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 2.64 (m, $(H3)_2$), 3.31 (m, $(H4)_2$), 4.16 (q, J = 7.1 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H), 4.28 (s, 2H), 5.05 (t, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.05, 14.35, 24.74, 27.76, 41.69, 59.65, 61.92, 92.10, 158.97, 166.49, 166.89, 176.47. Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.56; H, 6.85; N, 5.26.

(i) (±)-(*E*)-1-[1-(Ethoxycarbonyl)ethyl]-5-[(ethoxycarbonyl)methylidene]-2-pyrrolidinone (15b). General method A with keto amide **13b** (82 mg, 0.29 mmol) and a catalytic quantity of PTSA, in 1,2-dichloroethane (15 mL), and a reflux time of 24 h gave **15b**, 84%: bp 120 °C (1 mm); IR (film) 1740, 1710, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.52 (d, J = 7.3 Hz, 3H), 2.59 (t, J = 7.5 Hz, $(H3)_2$), 3.28 (m, $(H4)_2$), 4.15 (q, J = 7.1 Hz, 2H), 4.21 (m, 2H), 4.89 (q, J = 7.3 Hz, 1H), 5.10 (t, J = 2.0 Hz, 1H); ^{13}C

NMR ($CDCl_3$) δ 13.10, 13.98, 14.29, 24.65, 27.60, 49.18, 59.50, 61.77, 92.43, 157.76, 166.93, 169.14, 176.17. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.86; H, 6.85; N, 5.20.

(j) (±)-(*E*)-1-[1-(Ethoxycarbonyl)-3-methylbutyl]-5-[(ethoxycarbonyl)methylidene]-2-pyrrolidinone (15c). General method A with keto amide **13c** (155 mg, 0.47 mmol) and a catalytic quantity of PTSA, in 1,2-dichloroethane (15 mL), and a reflux time of 20 h gave **15c**, 84%: bp 155 °C (1 mm); IR (film) 1750, 1715, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, *J* = 4.6 Hz, 3H), 0.94 (d, *J* = 4.5 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.46 (m, 1H), 1.95 (t, *J* = 7.2 Hz, 2H), 2.60 (m, $(H3)_2$), 3.27 (m, $(H4)_2$), 4.14 (q, *J* = 7.2 Hz, 2H), 4.21 (m, 2H), 4.97 (t, *J* = 7.5 Hz, 1H), 5.10 (t, *J* = 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.96, 14.24, 21.54, 22.84, 24.48, 25.18, 27.56, 35.77, 52.05, 59.47, 61.67, 92.83, 157.94, 166.93, 169.17, 176.54. Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found C, 61.61; H 8.23; N, 4.65.

(k) (±)-(*E*)-1-[1-(Ethoxycarbonyl)-2-phenylethyl]-5-[(ethoxycarbonyl)methylidene]-2-pyrrolidinone (15d). General method A with keto amide **13d** (165 mg, 0.45 mmol) and a catalytic quantity of PTSA, in 1,2-dichloroethane (15 mL), and a reflux time of 24 h gave **15d**, 86%: bp 200 °C (1 mm); IR (film) 1745, 1710, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 2.29 (m, 1H), 2.46 (m, 1H), 3.13 (m, $(H4)_2$), 3.29 (dd, *J* = 10.8, 14.2 Hz, 1H), 3.45 (dd, *J* = 5.5, 14.1 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.25 (m, 2H), 5.09 (t, *J* = 8.0 Hz, 1H), 5.11 (t, *J* = 1.9 Hz, 1H), 7.13 (m, 2H), 7.24 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 13.95, 14.24, 24.40, 27.17, 32.90, 54.88, 59.45, 61.86, 92.69, 126.85, 128.32, 128.81, 136.17, 158.02, 166.85, 168.36, 176.18. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.99; H, 6.76; N, 4.23.

4,6-Dioxo-*N*-[6-(methoxycarbonyl)hexyl]-6-phenylhexamide (17) and 4-Hydroxy-*N*-[6-(methoxycarbonyl)hexyl]-6-oxohex-4-enamide (19). The enol lactone **16** (100 mg, 0.50 mmol, 1 equiv), methyl 7-aminoheptanoate[20] (126 mg, 0.64 mmol, 1.3 equiv), and triethylamine (85 μL, 0.64 mmol, 1.3 equiv) in CH_2Cl_2 (10 mL) were reacted according to the general method described for **13** to give a mixture of the keto amide **17** and the enol amide **19** in the ratio of 1:4, respectively, by ^1H NMR, 93%: FTIR (KBr) 3299, 1737, 1634, 1568 cm^{-1}; ^1H NMR ($CDCl_3$) enol amide **19** from mixture δ 1.31 (m, 4H), 1.49 (m, 2H), 1.60 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.54 (t, *J* = 6.9 Hz $(H2)_2$), 2.85 (t, *J* = 6.9 Hz, $(H3)_2$), 3.24 (m, NCH_2), 3.66 (s, 3H), 5.70 (brs, NH), 6.21 (s, 1H), 7.47 (m, 3H), 7.86 (m, 2H); selected ^1H NMR data ($CDCl_3$) for keto amide **17** δ 4.17 (s, 2H); HRMS calcd for $C_{20}H_{27}NO_5$ 361.1889, found 361.1899.

(*E*)-1-[(Methoxycarbonyl)hexyl]-5-(2-oxo-2-phenylethylidene)-2-pyrrolidinone[7] (18). A mixture of the enol amide **17** and the keto amide **19** (60 mg, 0.17 mmol), prepared as above, was refluxed of 43 h according to method A (see preparation of **15b**) to give **18**, 81%: mp 62–63 °C (ether/petroleum ether) (lit.[7] mp 60 °C).

(+)-(4*S*)-3-(Benzyloxycarbonyl)-4-[(chloroformyl)methyl]-1,3-oxazolidin-5-one (21). The acid[15] **21** (2.00 g, 7.2 mmol, 1 equiv) was dissolved in CH_2Cl_2 (60 mL), and the solution was cooled to 0 °C. Freshly distilled oxalyl chloride (3.1 mL, 35.8 mmol, 5 equiv) and a catalytic quantity of DMF were added. The mixture was stirred at 0 °C for 2 h and at 20 °C for 16 h. The solvent was evaporated, and more CH_2Cl_2 (2 mL) was added and evaporated (repeated three times). Final traces of oxalyl chloride were removed at 1 mm to yield the acid chloride **21** as a beige solid (2.15 g, 100%) which was used in subsequent steps without further purification: ^1H NMR ($CDCl_3$) δ 3.55 (d, *J* = 17.2 Hz, 1H), 3.86 (bm, 1H), 4.33 (m, H4), 5.17 and 5.23 (AB_q, *J* = 12.7 Hz), 5.34 (m, 1H, $(H2)_a$), 5.50 (brs, 1H, $(H2)_b$), 7.37 (m, 5H); $[\alpha]^{20}_D$ = +94° (CH_2Cl_2).

(+)-(4*S*)-3-(Benzyloxycarbonyl)-4-[3-(ethoxycarbonyl)-2-oxo-3-(triphenylphosphoranylidene)propyl]-1,3-oxazolidin-5-one (22). The acid chloride **21** (2.16 g, 7.2 mmol) was dissolved in CH_2Cl_2 (60 mL), and the solution was cooled to 0 °C. [(Ethoxycarbonyl)methylene]triphenylphosphorane (4.99 g, 14.3 mmol, 2 equiv) was added, and the solution was stirred at 0 °C for 30 min and at 20 °C for 30 min. The solvent was evaporated, and the residue was purified by radial chromatography, eluting with 55% ethyl acetate/45% petroleum ether to give **22** as a colorless solid (4.502 g, 100%): mp 73–75 °C (ether/petroleum ether, white powder): ^1H NMR ($CDCl_3$) δ 0.73 (bt, 3H), 3.39 (d, *J* = 17.5 Hz, 1H, C4-$(CH)_a$), 3.77 (q, *J* = 7.1 Hz, 2H), 4.20–4.32 (m, 3H, C4-$(CH)_b$, H4 and $(H2)_a$), 5.16 (m, 2H), 5.31 (d, *J* = 12.0 Hz, 1H, $(H2)_b$), 7.49 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 13.79, 41.20, 52.05, 58.34, 67.25, 71.72 (d, *J* = 109.7 Hz, C=PPh_3), 77.82, 126.23 (d, *J* = 93.7 Hz, C1 of Ph_3), 128.2 br, 128.42 (d, *J* = 12.1 Hz, *m*-C of Ph_3), 131.73 (d, *J* = 3.0 Hz, *p*-C of Ph_3), 133.21 (d, *J* = 10.0 Hz, *o*-C of Ph_3), 136.19, 152.42, 167.20 (d, *J* = 5.1 Hz), 173.42, 192.39 (d, *J* = 5.0 Hz); $[\alpha]^{20}_D$ = +100° (CH_2Cl_2). Anal. Calcd for $C_{35}H_{32}NO_7P$: C, 68.96; H, 5.29; N, 2.30. Found: C, 68.88; H, 5.36; N, 2.24.

(+)-(5*S*)-1-Ethyl-5-(benzyloxycarbonyl)amino]-3-oxo-2-(triphenylphosphoranylidene)hexanedioate (23). 1 N aqueous NaOH (35 mL, 34.4 mmol, 6 equiv) was added to a stirred solution of phosphorane **22** (3.50 g, 5.7 mmol) in methanol (70 mL), at 20 °C. After 4 h the solution was acidified to pH 3 with 1 N HCl, the solvent was evaporated, and the residue was extracted with ethyl acetate (2×). The combined ethyl acetate extracts were dried ($MgSO_4$), and the solvent was evaporated to give **23** (2.637 g, 77%): ^1H NMR ($CDCl_3$) δ 0.67 (t, *J* = 7.1 Hz, 3H), 3.13 (m, 1H, $(H4)_a$), 3.73 (m, 2H), 4.02 (m, 1H, $(H4)_b$), 4.55 (m, H5), 5.11 (m, 2H), 5.94 (d, *J* = 6.5 Hz, NH), 7.29–7.69 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 13.31, 42.25 (d, *J* = 7.1 Hz), 50.33, 59.02, 66.42, 74.53 (d, *J* = 107.8 Hz, C=PPh_3), 125.19 (d, *J* = 93.6 Hz, C1 of Ph_3), 127.67, 127.77, 128.23, 128.77 (d, *J* = 12.1 Hz, *m*-C of Ph_3), 132.12 (d, *J* = 2.0 Hz, *p*-C of Ph_3), 132.88 (d, *J* = 10.1 Hz, *o*-C of Ph_3), 136.21, 155.38, 166.88 (d, *J* = 13.1 Hz), 173.34, 194.33 (d, *J* = 3.1 Hz); $[\alpha]^{20}_D$ = +64° (CH_2Cl_2).

(−)-(4*S*,*E*)-Ethyl 3-[(Benzyloxycarbonyl)amino]-5-[(ethoxycarbonyl)methylidene]-2-tetrahydrofuranone (24). The acid **23** (1.57 g, 2.6 mmol) was dissolved in THF (150 mL) and refluxed for 48 h. The solvent was evaporated, and the residue was purified by radial chromatography using a 4 mm silica gel chromatotron plate, eluting with 75% CH_2Cl_2/25% ethyl acetate to give **24** (680 mg, 82%): mp 118–120 °C (ethyl acetate/petroleum ether, white crystals): ^1H NMR ($CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3H), 3.25 (dd, *J* = 7.4, 18.5 Hz, 1H, $(H4)_a$), 3.89 (dd, *J* = 10.5, 18.5 Hz, 1H, $(H4)_b$), 4.18 (q, *J* = 7.2 Hz, 2H), 4.36 (brq, *J* = 9.4 Hz, H3), 5.13 (m, 2H), 5.56 (brs, NH), 5.74 (s, =CH), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.17, 33.10, 48.91, 60.30, 67.62, 98.59, 128.22, 128.43, 128.58, 135.51, 155.73, 164.02, 166.29, 171.74; $[\alpha]^{20}_D$ = −73° (CH_2Cl_2). Anal. Calcd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.33; H, 5.07; N, 4.41.

(+)-(5*S*)-Ethyl 5-[(Benzyloxycarbonyl)amino]-5-[*N*-[1-(ethoxycarbonyl)methyl]carbamoyl]-3-oxopentanoate (25). Glycine ethyl ester hydrochloride (105 mg, 0.75 mmol, 1.2 equiv) and triethylamine (99 μL, 0.75 mmol, 1.2 equiv) were added to enol lactone **24** (200 mg, 0.63 mmol), dissolved in CH_2Cl_2 (100 mL), and the mixture was stirred at 20 °C for 16 h. The solution was washed with H_2O and dried ($MgSO_4$) and the solvent evaporated to give **25** as a white solid (251 mg, 95%) which was used in subsequent steps without further purification: FTIR (film) 3344, 1720, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 2.95 (dd, *J* = 6.0, 18.0 Hz, 1H, $(H4)_a$), 3.29 (dd, *J* = 4.0, 18.0 Hz, 1H, $(H4)_b$), 3.50 (s, $(H2)_2$), 3.98 (dd, *J* = 1.8, 5.4 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.66 (m, H5), 5.13 (s, 2H), 5.94 (d, *J* = 8.4 Hz, CBzNH), 6.97 (brs, $NHCH_2$), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.03, 14.09, 41.50, 44.00, 49.37, 50.86, 61.53, 61.58, 67.37, 128.14, 128.30, 128.57, 135.90, 156.13, 166.70, 169.29, 170.66, 202.26; $[\alpha]^{20}_D$ = +5° (CH_2Cl_2); HRMS calcd for $C_{20}H_{28}N_2O_8$ 422.1689, found 422.1693.

(−)-(3*S*,*E*)- and (3*S*,*Z*)-3-[(Benzyloxycarbonyl)amino]-1-[(ethoxycarbonyl)methyl]-5-[(ethoxycarbonyl)methylidene]-2-pyrrolidinone (26a) and (26b). A solution of the keto amide **25** (250 mg, 5.9 mmol) and PTSA (50 mg) in 1,2-dichloroethane (100 mL) was refluxed, with azeotropic removal of H_2O, for 4 h. The solution was cooled to 20 °C, washed with H_2O, and dried ($MgSO_4$) and the solvent evaporated to a yellow

(20) Eck, J. C. *Organic Syntheses*; John Wiley and Sons: New York, 1943; Collect. Vol. III, p 28; *Chem. Abstr.* **1953**, *53*, 19901i.

oil which solidified on standing at 0 °C. Purification by radial chromatography using a 2 mm silica gel chromatotron plate, eluting with 70% CH_2Cl_2/30% ethyl acetate, gave **26b** as an oil (9%): ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7 Hz, 3H), 1.27 (t, J = 7 Hz, 3H), 2.60 (m, $(H4)_2$), 4.01 and 4.45 (ABq, J = 18 Hz, 2H), 4.18 (2 × q, 4H), 4.64 (dt, J = 6.8, 2.0 Hz, H3), 5.20 (s, 2H), 6.81 (brs, NH), 7.10 (brs, =CH), 7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.09, 36.82, 42.65, 56.82, 61.15, 61.55, 67.50, 119.10, 128.14, 128.46, 128.65, 129.98, 135.56, 153.11, 166.79, 168.65, 170.34; HRMS calcd for $C_{20}H_{24}N_2O_7$ 404.1583, found 404.1583. Further elution gave **26a** (58%): mp 143–146 °C (ethyl acetate/petroleum ether, white crystals); FTIR (film) 3350, 1801, 1714, 1632, 1530 cm^{-1}; $[\alpha]^{20}_D = -81°$ (CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 3.11 (dd, J = 6.9, 19.0 Hz, 1H, $(H4)_a$), 3.91 (dd, J = 9.7, 19.0 Hz, 1H, $(H4)_b$), 4.12–4.26 (m, 5H), 4.36 (m, H3), 4.46 (d, J = 17.6 Hz, 1H), 5.12 (m, 3H, CH_2Ph, =CH), 5.55 (brs, NH), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.07, 14.36, 32.85, 42.11, 50.06, 59.92, 62.12, 67.39, 93.50, 128.19, 128.33, 128.58, 128.64, 154.84, 155.78, 166.27, 166.49, 173.74; $[\alpha]^{20}_D = -101°$ (CH_2Cl_2). Anal. Calcd for $C_{20}H_{24}N_2O_7$: C, 59.40; H, 5.98; N, 6.93. Found: C, 59.54; H, 5.89; N, 7.13.

(±)-Ethyl 2-Chloro-5-[*N*-[1-(ethoxycarbonyl)methyl]-carbamoyl]-3-oxopentanoate (30) and 5-[Chloro(ethoxycarbonyl)methyl]-1-[(ethoxycarbonyl)methyl]-5-hydroxy-2-pyrrolidinone (31). Glycine ethyl ester hydrochloride (27 mg, 0.19 mmol, 1.3 equiv) and triethylamine (25 μL, 0.19 mmol, 1.3 equiv) were added to enol lactone **29**[18] (30 mg, 0.15 mmol, 1 equiv), dissolved in ethyl acetate (3 mL), and the mixture was stirred for 3 h. The solvent was evaporated to give an oil which contained, by ^1H NMR, keto amide **30** and hydroxy lactam **31** in the ratio 9:1, respectively: ^1H NMR ($CDCl_3$) keto amide **30** from mixture δ 1.29 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 2.60 (t, J = 6.5 Hz, $(H5)_2$), 3.07 (m, $(H4)_2$), 4.02 (d, J = 5.2 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 4.90 (s, 1H), 6.10 (brs, NH). Ethyl acetate (3 mL) was added to the residue, the mixture was filtered, and the solvent was evaporated to give an oil (47 mg, quant) which contained, by ^1H NMR, keto amide **30** and hydroxy lactam **31** in the ratio 3:7, respectively. Hydroxy lactam **31** was present as a mixture of diastereoisomers by ^1H NMR;^1H NMR ($CDCl_3$) hydroxy lactam **31** from mixture δ 1.26–1.40 (m, 3H), 2.17, 2.48, 2.68 and 2.89 (m, H3 and H4), 3.71 and 4.68 (AB_q, J = 18.1 Hz), 4.13 and 4.50 (AB_q, J_{AB} = 17.8 Hz), 4.20–4.32 (m, OCH_2), 4.38 (s, CHCl), 4.53 (s, CHCl).

***(E)*- and *(Z)*-5-[Chloro(ethoxycarbonyl)methylidene]-1-[(ethoxycarbonyl)methyl]-2-pyrrolidinone (28a) and (28b). Method A.** The keto amide and hydroxy lactam mixture (**30** and **31**) from above (32 mg, 0.10 mmol) and a catalytic quantity of PTSA were dissolved in 1,2-dichloroethane (10 mL). Activated 4 Å molecular sieves were added, and the mixture was stirred at 70 °C for 6.5 days. The mixture was cooled to 20 °C and filtered and the solvent evaporated. Purification by radial chromatography eluting with 72% petroleum ether/22% ethyl acetate/6% CH_2Cl_2 gave **28a**, 13%: IR (film) 3435, 1740, 1720, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H), 2.64 (m, $(H3)_2$), 3.00 (m, $(H4)_2$), 4.19 (q, J = 7.2 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 4.68 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.06, 14.09, 27.19, 28.19, 45.22, 61.46, 61.94, 99.73, 150.21, 162.81, 167.75, 177.79; HRMS calcd for $C_{12}H_{16}{}^{37}ClNO_5$ 291.0688, found 291.0702. Further elution gave **28b**, 13%: IR (film) 3465, 1740, 1690, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H), 2.64 (m, $(H3)_2$), 3.35 (m, $(H4)_2$), 4.24 (q, J = 7.1 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 4.86 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.11, 14.22, 27.76, 27.76, 44.63, 61.46, 61.80, 97.22, 152.26, 163.95, 167.92, 177.42; HRMS calcd for $C_{12}H_{16}{}^{37}ClNO_5$ 291.0688, found 291.0640. Further elution gave the imide **27**, 57%: mp 65–68 °C (ethyl acetate/petroleum ether, white crystals) (lit.[21] 68 °C). Anal. Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.99; N, 7.56. Found: C, 51.77; H, 5.87; N, 7.55. **Method B.** Acetic anhydride (36 μL, 0.38 mmol, 2 equiv) and triethylamine (50 μL, 0.38 mmol, 2 equiv) were added to a mixture of the keto amide **30** and the hydroxy lactam **31** (58 mg, 0.19 mmol, 1 equiv) and 4-DMAP (35 mg, 0.28 mmol, 1.5 equiv), dissolved in CH_2Cl_2 (6 mL), and the mixture was stirred for 2.5 h. The solvent was evaporated, and the residue was dissolved in benzene (10 mL), washed successively with 0.1 N HCl (4 × 10 mL) and 0.2 N NaOH (4 × 10 mL), and dried ($MgSO_4$), and the solvent was evaporated to yield **33**, 65%, as a mixture of diastereoisomers in a ratio of 3:2 by ^1H NMR. This oil was used in subsequent steps without further purification: IR (film) 1750, 1725, 1635, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) both diastereoisomers δ 1.25–1.36 (m, 12H, 4 × CH_3), 2.01 (s, major diastereoisomer, $COCH_3$), 2.06 (s, 3H), 2.40–2.52 (m, 4H), 2.74–2.98 (m, 4H), 3.82–4.32 (m, 12H), 4.88 (s, major, 1H), 5.00 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.87, 13.96, 14.05, 21.57, 21.69, 26.69, 27.88, 28.44, 28.61, 41.80, 42.52, 56.67, 58.38, 61.43, 61.49, 62.61, 62.76, 96.04, 96.91, 165.91, 165.77, 166.00, 167.87, 167.97, 168.93, 169.53, 176.39, 176.52; HRMS calcd for $C_{12}H_{16}{}^{35}ClNO_5$ 289.0718, found 289.0715. The acetate **33** (40 mg, 0.11 mmol) was dissolved in benzene (5 mL) and heated at 65 °C for 90 min. Chromatograrhy on silica gave the *(E)*- and *(Z)*-enamino esters **28a** and **28b**, respectively (78%), and compounds **32** (15%). Compounds **28** gave **32** on distillation (145–160 °C, 1 mm); ^1H NMR ($CDCl_3$) *(E)*-isomer **32a** from mixture δ 1.28 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H), 4.19 (q, J = 7.2 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 4.35 (s, 2H), 5.44 (d, J = 1.0 Hz, 1H), 6.40 (dd, J = 1.5, 6.0 Hz, H3), 8.21 (d, J = 6.0 Hz, H4); *(Z)*-isomer **32b** from mixture δ 1.27 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 4.17 (q, J = 7.2 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 4.94 (s, 2H), 5.44 (s, 1H), 6.36 (d, J = 5.7 Hz, H3), 6.99 (d, J = 5.7 Hz, H4); ^{13}C NMR ($CDCl_3$) **32a** from mixture δ 14.09, 14.24, 40.56, 60.74, 61.88, 99.69, 126.73, 136.43, 150.48, 165.24, 167.34, 169.79; HRMS calcd for $C_{12}H_{15}NO_5$ 253.0951, found 253.0953.

Supplementary Material Available: ^1H NMR spectra of compounds **6a**, **7a**, **8e,f**, **11a,b**, **12a,b**, **13a–d**, **17**, **19**, **21**, **23**, **25**, **26b**, **28a,b**, **30**, **31**, **32a,b**, and **33** (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO941216K

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