Synthesis of Lactam-Based Peptidomimetics from β-Keto Esters and β-Keto Amides

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Pyrrolidinone-based peptidomimetics, in which the peptide bond is forced to adopt either a cis or trans geometry, have been prepared from readily available amino acids. Peptidomimetics based on amino acid side chain to side chain cyclization (**17**), side chain to N cyclization (**18**), and α-H to side chain cyclization (**28**) have been developed. A key step in the syntheses is the treatment of a peptide-based β-keto ester or amide with an amine. The absolute configuration of compounds **28** was established using Seebach oxazolidinone chemistry.

A good deal of effort has been invested in the design and synthesis of modified peptides (peptidomimetics) in an attempt to alleviate problems that are associated with using peptides as drugs. These problems include poor bioavailability, bioselectivity, and biostability and also the fact that it is often only a particular conformation of a peptide that is responsible for its biological activity and hence function.[1,2] As an example, conformationally defined cyclic amino acid mimetics have been incorporated into peptides to provide peptidomimetics with reduced conformational mobility.[1,2] Freidinger lactams, peptidomimetics in which either the α-H or α-C of an amino acid residue of a peptide is cyclized onto the nitrogen of the adjacent C-terminal amino acid, provide a specific example.[3−5]

Compounds **1** and **2** (Figure 1) represent important examples of both nitrogen to α-C and nitrogen to α-H cyclizations where the peptide bond is forced, by the constraints of the five-membered ring, to adopt a trans peptide bond geometry.[6,7] (The trans/cis notation refers to the relationship between the two peptide bond side chains and ignores the higher priority of the carbonyl group.) The alternative cis peptide bond mimetics of type **5**, resulting from cyclization of the two amino acid side chains, are also known but have received far less attention.[3,8] A number of alternative structures have, however, been developed as cis peptide bond isosteres, e.g., simple *N*-methyl amino acids[9] and the more elaborate examples shown in Figure 2.[10,11] In some cases, e.g., **7**, the amino acid backbone has been modified to yield a specific enzyme inhibitor.[11]

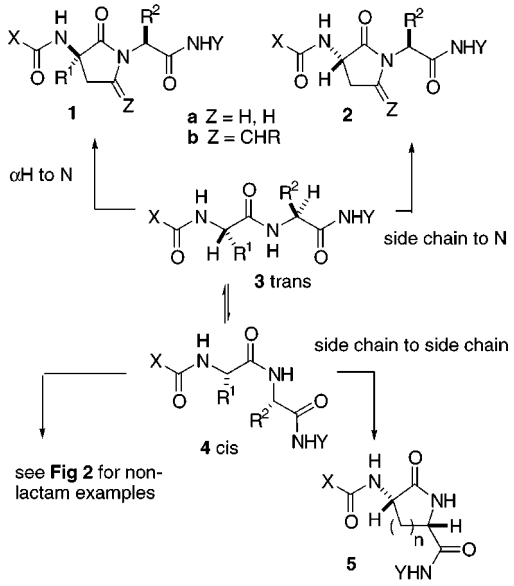

Figure 1. Lactam-based peptidomimetics incorporating either a trans or cis peptide bond isostere.

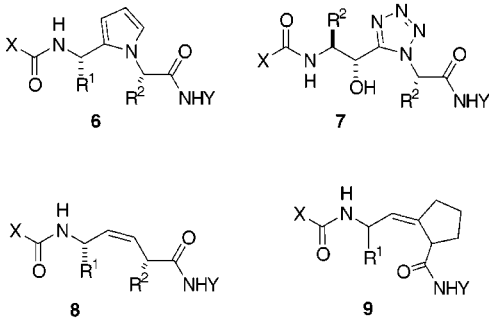

Figure 2. Other cis peptide bond peptidomimetics.

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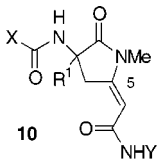
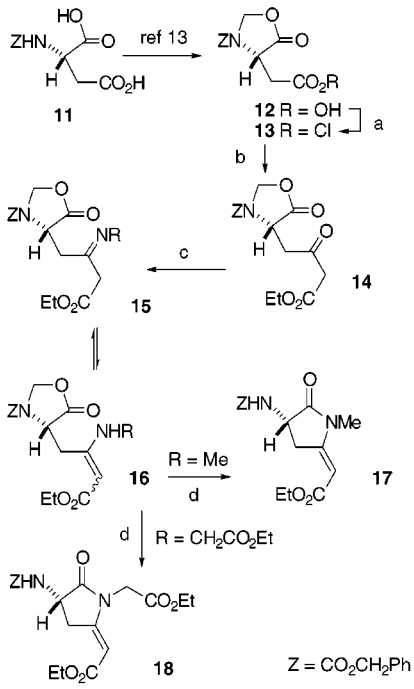


a R^1 = H (side chain to side chain cyclisation)
b R^1 = CH_2Ph (αH to side chain cyclisation)

Figure 3. Modified cis peptide bond peptidomimetics.

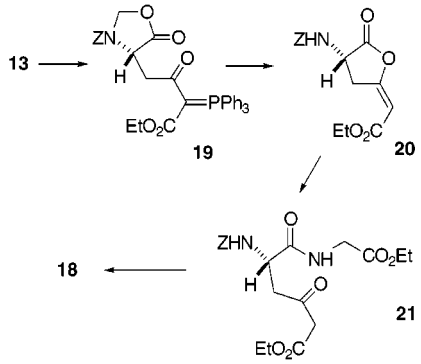
Scheme 1[a]



[a]Key: (a) $(COCl)_2$, DMF, DCM; (b) Meldrum's acid, pyr, DCM then EtOH, reflux (87%); (c) $MeNH_2$, 1,2-DCE, reflux; or gly-OEt.HCl, Et_3N, benzene, reflux; (d) 150 °C, 1 mm, 1 h (70% for **17**, 63% for **18**).

In this paper, we present a convenient synthesis of cis peptide bond mimetics of the general type **10** (Figure 3; for a specific example see **17**). These peptidomimetics possess an extended planar backbone, as compared to **5**, with the inclusion of a methylidene linker at C5. The *N*-methyl group was incorporated into the structure by analogy with *N*-methylpeptides[9] that are known to adopt an analogous cis conformation and also for ease of synthesis. In addition, we report a preparation of the related trans peptide bond lactam-based mimetic **18** (an example of **2b**) from **14**, a common synthetic precursor to **17** (Scheme 1). This study is part of our ongoing work to produce a library of lactam-based peptidomimetics that possess well-defined reactivity and conformation.[7] The cis peptide bond mimetics were conveniently prepared from readily available amino acids—aspartic acid for the side chain to side chain cyclic mimetics (see **10a** and Scheme 1) and, in the case of α-H to side chain cyclization, by employing Seebach oxazolidinone chemistry[12]

Scheme 2[a]



[a] See ref 13.

(see **10b** and Scheme 3). Some related synthetic studies have been published by us[13] and others.[14] Initial work on derivatizing these peptidomimetics (see Scheme 4) is also presented.

Results and Discussion

The side chain to side chain cyclic mimetics **10a** were prepared as detailed in Scheme 1. To this end, the L-aspartic acid derived oxazolidinone **12**[13] was converted into the corresponding acid chloride **13** on treatment with oxalyl chloride and a catalytic amount of DMF. Reaction with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and pyridine in dichloromethane, followed by refluxing in dry ethanol, gave **14**. The β-keto ester **14** was then refluxed in 1,2-dichloroethane containing an excess of methylamine to give an oil that consisted of a mixture of compounds tentatively assigned as **15** and **16** (the ^{1}H NMR spectrum of this mixture was complex and could not be assigned). The mixture was then heated (150 °C) at 1 mmHg, and the resulting material was purified by chromatography to give the desired lactam **17** in good yield.

Treatment of **14** with glycine ethyl ester (Scheme 1), rather than methylamine, gave **16** (R = CH_2CO_2Et) as an intermediate to the alternative trans peptide bond mimetic **18**, an example of **2b**. Compound **18** can also be prepared using an alternative phosphorane-based approach (Scheme 2), and its peptide sequence has been extended in the C-direction.[13] Some interesting comparisons can be made between the sequences shown in Schemes 1 and 2. In the second series, **13** is reacted with ethoxycarbonylmethylenetriphenylphosphorane rather than Meldrum's acid, and the resulting phosphorane **19** gives rise to the enol lactone **20** on hydrolysis of the oxazolidinone followed by heating. Insertion of the desired amino acid into the ring is then achieved via the intermediacy of the amide **21**, rather than the imine/enamine **15/16** in the sequence shown in Scheme 1. (Cyclization of an amide of this type is also central to the synthetic procedure discussed in ref 14a.) The intermediates from both sequences then cyclize to give the same product, **18**. In the next series of reactions, the α-H to side chain cis peptidomimetic **28** (an example of general structure **10b**) was prepared as detailed in

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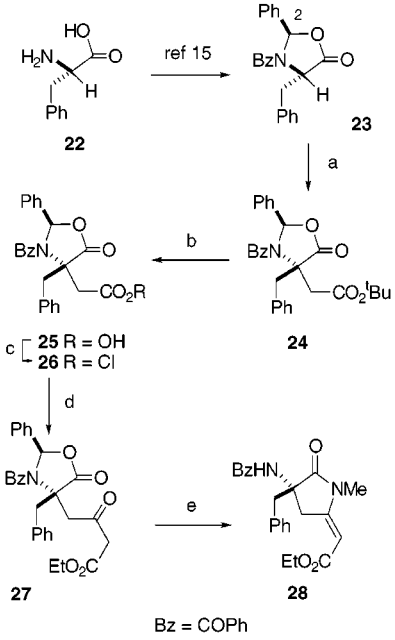
Scheme 3[a]

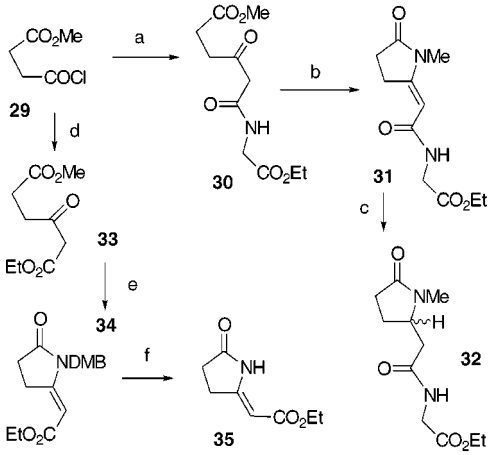


[a]Key: (a) LiHMDS, THF, -78 °C then $BrCH_2CO_2{}^tBu$ (87%); (b) DCM, TFA, O °C (41%); (c) $(COCl)_2$, DMF, DCM; (d) Meldrum's acid, pyr, DCM then EtOH, reflux (73%); (e) $MeNH_2$, 1,2-DCE, reflux then 150 °C, 1 mm, 1 h (43%).

Scheme 3. The syn oxazolidinone **23** was prepared from L-phenylalanine **22**, according to literature-based methods.[15] Alkylation of the enolate derived from **23** with *tert*-butylbromoacetate gave **24**, the absolute configuration of which was established by a combination of an X-ray crystal structure determination, the known absolute configuration of the starting amino acid **22**, and the fact that alkylation occurs opposed to the C2 phenyl group in the preparation of **24**. A sequence involving removal of the *tert*-butyl protecting group, subsequent conversion into the acid chloride **26**, coupling with Meldrum's acid, and finally refluxing with ethanol gave **27** in good yield. This was then reacted with methylamine, as per **14**, and the imine/enamine mixture was heated at 1 mmHg to give the desired peptidomimetic **28**.

Next we chose to investigate a number of synthetic approaches for the selective modification and extension of these peptidomimetics. Simple model compounds, derived from the acid chloride **29**, were chosen for this preliminary study (Scheme 4). First, we demonstrated that the peptide sequence of the peptidomimetics can be extended in the C-direction by preparing a β-keto amide[16] (**30**), rather than a β-keto ester (**14** or **27**), using ethyl glycine in place of ethanol (compare Scheme 4 step a with Scheme 1 step b). Reaction of **30** with methylamine, as described for **14**, then gave the extended peptide structure **31**. This compound was also reduced by catalytic hydrogenation to give the saturated analogue **32**. Finally, the preparation of compounds **10**, in which the *N*-methyl group is replaced by an NH group, was investigated. These compounds not only better resemble the natural parent peptides but also provide access to peptidomimetics that possess the alternative (*Z*)-geometry (for example see **35**). Reaction of the β-keto ester **33** with 2,4-dimethoxybenzylamine (DMB) gave the N-protected derivative **34**, which was deprotected to give **35** as the (*Z*)-isomer, which is known[17] to be thermodynamically more stable than the corresponding (*E*)-isomer as a result of intramolecular hydrogen bonding between the NH and carbonyl groups. Future work will involve extending these preliminary studies to the more complex examples, derived from **14** and **27**.

Scheme 4[a]



[a]Key: (a) Meldrum's acid, pyr, DCM then gly-OEt.HCl, Et_3N, benzene, reflux (47%); (b) $MeNH_2$, 1,2-DCE, reflux (25%); (c) Pd on C, MeOH, H_2 (84%); (d) Meldrum's acid, pyr, DCM then EtOH, reflux; (e) DMB.HCl, Et_3N, 1,2-DCE, reflux (38%); (f) CAN, acetone, MeOH (50%).

In summary, we have developed a convenient and versatile synthetic route to lactam-based peptidomimetics in which the peptide bond is forced to adopt a cis geometry. The sequence is amenable to either side chain to side chain mimetics (**10a** and **17**) or α-H to side chain mimetics (**10b** and **28**). The synthetic methodology is applicable to a range of amino acid starting materials and the absolute configuration of the mimetics is controllable using Seebach-based oxazolidinone chemistry.[12] Access to some related trans peptide bond surrogates and some preliminary studies on the extension and modification of the structures are also presented.

Experimental Section

General Methods. NMR spectra were recorded on a Varian Unity 300 spectrometer in the specified solvent and at a probe temperature of 23 °C. Radial chromatography was carried out using a Chromatotron (Harrison Research Inc.) using glass plates coated with Merk type 60 PF_{254} silica gel. All other details were as previously reported.[18]

4(*S*)-Ethyl 4-(3-Benzyloxycarbonyl-5-oxo-1,3-oxazolidin-4-yl)-3-oxobutanoate 14. 4(*S*)-3-Benzyloxycarbonyl-5-oxo-oxazolidin-4-yl acetic acid[19] **12** (1.75 g, 6.3 mmol) was dissolved in dichloromethane (40 mL), and the solution was cooled to 0 °C. Freshly distilled oxalyl chloride (2.72 mL, 31.3 mmol, 5 equiv) and a catalytic quantity of dimethylformamide

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(18) Abell, A. D.; Nabbs, B. K.; Battersby, A. R. *J. Org. Chem.* **1998**, *63*, 8163.
(19) Scholtz, J. M.; Bartlett, P. A. *Synthesis* **1989**, 542.

were added, and the mixture was stirred at 0 °C for 2 h and at 20 °C for 16 h. The solvent was removed under reduced pressure. Dichloromethane (2 mL) was added and then removed under reduced pressure. This was repeated twice more, and the residue was left at 1 mmHg until required. A sample of the above acid chloride **13** (100 mg) in dichloromethane (2 mL) was added dropwise, over 10 min, to an ice-cooled solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (51 mg, 0.35 mmol) in dichloromethane (2 mL) containing dry pyridine (0.136 mL, 1.7 mmol). The mixture was stirred at ice temperature for 50 min and then at 20 °C for 45 min. The resulting red-purple solution was poured into 2 N aqueous HCl (2 mL) containing crushed ice. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 mL). The combined dichloromethane extracts were washed with 2 N HCl (2 mL) and saturated aqueous NaCl (1 mL), dried, and evaporated to dryness under reduced pressure. The resulting mixture was refluxed in dry ethanol for 2.5 h. The solvent was removed under reduced pressure to give a red-purple oil, which was purified by radial chromatography (dichloromethane/ethyl acetate, 4:1) to give **14** as a yellow oil (0.102 g, 87%): IR (KBr) 1801, 1717 (br) cm^{-1}; $[\alpha]^{20}_D = +100°$ (CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.28 (t, $J = 7.0$ Hz, 3H), 3.20 (br d, $J = 18.3$ Hz, 1H), 3.244 (br, 2H), 3.62 (br, 1H), 4.18 (q, $J = 7.0$ Hz, 2H), 4.30 (br s, 1H), 5.19 (m, 2H), 5.38 (br d, $J = 3.5$ Hz, 1H), 5.51 (br, 1H), 7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.9, 40.9, 46.0, 51.4, 61.8, 68.1, 78.4, 128.2, 128.57, 128.62, 135.1, 152,7, 166.9, 170.9, 200.0; HRMS calcd for $C_{17}H_{19}NO_7$ 372.1048, found 372.1059.

(3*S*,*E*)-3-Benzyloxycarbonylamino-5-ethoxycarbonylmethylidene-1-methyl-2-pyrrolidinone 17. A solution of **14** (21 mg, 0.1 mmol) and methylamine (170 μL of a 7.1 M solution of methylamine in 1,2-dichloroethane, 1.2 mmol) was refluxed in 1,2-dichloroethane (10 mL) for 90 min. The volitiles were removed under reduced pressure to give a mixture tentatively assigned as a mixture of **15** and **16** (R = CH_2CO_2Et, ^1H NMR could not be assigned). This mixture was then heated (150 °C) at 1 mmHg for 1 h. Purification of the residue by radial chromatography (dichloromethane/ethyl acetate, 4:1) gave **17** as an oil (14 mg, 70%): ^1H NMR ($CDCl_3$) δ 1.28 (t, $J = 7.3$ Hz, 3H), 2.00−3.10 (br, 4H), 3.82 (dd, $J = 18.7$ and 9.3 Hz, 1H), 4.18 (q, $J = 7.3$ Hz, 2H), 4.38 (m, 1H), 5.12 (AB_q, $J_{AB} = 6.4$ Hz, 2H), 5.21 (s, 1H), 5.49 (br d, $J = 5.4$ Hz, 1H, NH), 7.34 (br, 5H); ^{13}C NMR ($CDCl_3$) δ 14.4, 27.4, 32.7, 50.2, 59.7, 67.3, 93.0, 128.1, 128.3, 128.5, 138.0, 155.2, 156.4, 166.8, 174.0; HRMS calcd for $C_{17}H_{20}N_2O_5$ 332.1372, found 332.1375.

***(*3*S*,*E*)-3-Benzyloxycarbonylamino-1-ethoxycarbonylmethyl-5-ethoxy-carbonylmethylidene-2-pyrrolidinone 18.** Glycine ethyl ester hydrochloride (73 mg, 0.5 mmol) and triethylamine (73 μL, 0.5 mmol) were added to **14** (61 mg, 0.2 mmol) dissolved in benzene (10 mL), and the mixture was heated at reflux, with azeotropic removal of water, for 90 min. The mixture was filtered, and the solvent was removed by rotary evaporation. The residue was then heated (150 °C) at 1 mmHg for 1 h. The residue was purified by radial chromatography using a 1 mm silica gel chromatatron plate (dichloromethane/ethyl acetate, 4:1) to give **18**[13] (44 mg, 63%). [α]D = −101° (CH_2Cl_2).

(2*R*,4*S*)-*tert*-Butyl 3-Benzoyl-4-benzyl-5-oxo-2-phenyl-1,3-oxazol-idin-4-yl Ethanoate 24. The oxozolidinone **23**[15] (200 mg, 0.6 mmol) was dissolved in THF (20 mL), and the solution was cooled to −78 °C. LiHMDS (0.68 mL of a 1 M solution in THF, 0.7 mmol, 1.2 equiv) was added, and the resulting yellow solution was stirred at −78 °C for 7 min. *tert*-Butylbromoacetate (0.1 mL, 0.6 mmol) was added, and the solution was stirred at −78 °C for 2 h. The solution was allowed to warm to room temperature, stirred for an additional 16 h, and then partitioned between saturated aqueous NH_4Cl (15 mL) and ether (10 mL). The aqueous layer was separated and extracted with ether (10 mL). The combined ether extracts were washed with water (2 × 5 mL), dried, and evaporated to give **24** as a pale yellow solid (217 mg, 87%): mp 180−181 °C; IR (KBr) 1791.7, 1720.4, 1654.8 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (s, 9H), 3.11 and 3.95 (AB_q, $J_{AB} = 17.8$ Hz, 2H), 3.35 and 3.98 (AB_q, $J_{AB} = 13.6$ Hz, 2H), 5.55(d, $J = 7.8$ Hz, 2H), 6.49 (s, 1H), 6.67 (t, $J = 7.8$ Hz, 2H), 6.82 (d, $J = 7.4$ Hz, 2H), 6.95 (t, $J = 7.6$ Hz, 1H), 7.06 (t, $J = 7.4$ Hz, 2H), 7.17 (t, $J = 7.4$ Hz, 1H), 7.41 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 28.0, 40.3, 42.3, 66.3, 82.2, 91.5, 125.3, 127.7, 127.7, 127.9, 128.2, 128.9, 128.1, 129.3, 130.9, 134.6, 135.3, 136.6, 169.7, 170.1, 173.2. Anal. Calcd for $C_{29}H_{29}NO_5$: C, 73.87; H, 6.20; N, 2.97. Found: C, 74.07; H, 6.24; N, 2.85.

(2*R*,4*S*)-Ethyl 4-(3-Benzoyl-4-benzyl-5-oxo-2-phenyl-1,3-oxazolidin-4-yl) 3-Oxobutanoate 27. The oxazolidinone **24** (500 mg, 1.1 mmol) was dissolved in dichloromethane (5 mL) and cooled to 0 °C. TFA (13.7 mL) was added, and the solution was stirred at 0 °C for 5 min. The solution was then diluted with dichloromethane (1 mL), washed with water (3 × 11.5 mL), and extracted with 5% aqueous $NaHCO_3$ (2 × 10 mL). The $NaHCO_3$ extracts were combined, cooled to 0 °C, acidified to pH 2 (universal indicator paper) with 1 N aqueous HCl, and extracted with ethyl acetate (3 × 15 mL). The combined ethyl acetate extracts were dried, and the solvent was removed under reduced pressure to give **25** as a white solid (179 mg, 41%): mp 207−210 °C (lit.[15] mp 207.5−211 °C).

The acid chloride **26** (262 mg, 0.6 mmol), prepared from **25** (240 mg, 0.6 mmol) using the method described for **13**, was reacted with Meldrum's acid (96 mg, 0.7 mmol) and dry pyridine (154 μL, 1.5 mmol) according to the method described in the preparation of **14**. The resulting residue was then treated with dry ethanol (as described for **14**), and the product was purified by radial chromatography (ethyl acetate/petroleum ether, 3:7) to give **27** as a yellow oil (203 mg, 73%): mp 103−104 °C (ethyl acetate/petroleum ether); $[\alpha]_D = +67°$ (CH_2Cl_2); IR (KBr) 1794, 1743, 1716, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, $J = 7.3$ Hz, 3H), 3.34 and 3.96 (AB_q, $J_{AB} = 13.5$ Hz, 2H), 3.39 and 4.39 (AB_q, $J_{AB} = 19.0$ Hz, 2H), 3.54 and 3.59 (AB_q, $J_{AB} = 15.6$ Hz, 2H), 4.22 (q, $J = 7.3$ Hz, 2H), 5.54 (d, $J = 7.3$ Hz, 2H), 6.49 (s, 1H), 6.68 (m, 2H), 6.78 (m, 2H), 6.96 (m, 1H), 7.05 (m, 2H), 7.17 (m, 1H), 7.38−7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.0, 42.2, 48.0, 49.0, 61.9, 65.4, 91.6, 125.3, 127.7, 127.9, 128.0, 128.2, 129.0, 129.2, 129.4, 130.9, 134.5, 135.0, 136.3, 166.1, 170.0, 173.0, 201.3; HRMS (FAB, M + 1) calcd for $C_{29}H_{28}NO_6$ 486.1917, found 486.1915.

(3*S*,*E*)-3-Benzoylamino-3-benzyl-5-ethoxycarbonylmethylidene-1-methyl-2-pyrrolidinone 28. Compound **27** (50 mg, 0.1 mmol) was treated with methylamine (340 μL of a 6 M solution in 1,2-dichloroethane, 20 equiv) as described for **17**. The solvent was removed under reduced pressure, and the residue was heated (150 °C) at 1 mmHg for 1 h. The residue was purified by radial chromatography (dichloromethane/ethyl acetate, 9:1) to give **28** as a white solid (17 mg, 43%): mp 231−232 °C; IR (KBr) 1736, 1692, 1655, 1618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, $J = 7.3$ Hz, 3H), 2.87 (s, 3H), 3.12 (s, 2H), 3.39 (dd, $J = 18.8$ and 2.0 Hz, 1H), 3.81 (dd, $J = 20.5$ and 1.0 Hz, 1H), 4.09 (m, 2H), 4.91 (br t, $J = 1.5$ Hz, 1H), 6.74 (s, 1H, NH), 7.16−7.26 (m, 5H), 7.38 (m, 2H), 7.46 (m, 1H), 7.70 (dd, $J = 6.9$ and 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.4, 27.1, 36.5, 42.8, 59.5, 59.7, 91.8, 127.0, 127.8, 128.6, 128.6, 129.9, 132.0, 133.1, 133.2, 156.4, 166.6, 166.8, 175.8; HRMS calcd for $C_{23}H_{24}N_2O_4$ 392.1737, found 392.1745.

Methyl 4,6-Dioxo-6-(ethoxycarbonylmethylamino)hexanoate 30. 3-Carbomethoxypropionyl chloride **29** (0.42 mL, 3.3 mmol) was treated with Meldrum's acid (500 mg, 3.5 mmol) as described in the preparation of **14**. The residue was treated with glycine ethyl ester (0.42 g, 3 mmol) and triethylamine (0.42 mL, 3 mmol) in dry benzene (25 mL) at reflux for 4 h. Evaporation under reduced pressure and purification of the residue by radial chromatography (petroleum ether/ethyl acetate, 5:3) gave **30** as a pale yellow oil (383 mg, 47%): IR (KBr) 3354, 1739 (br), 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (t, $J = 7.0$ Hz, 3H), 2.63 (t, $J = 6.4$ Hz, 2H), 2.87 (t, $J = 6.4$ Hz, 2H), 3.54 (s, 2H), 3.69 (s, 3H), 4.05 (d, $J = 5.6$ Hz, 2H), 4.22 (q, $J = 7.0$ Hz, 2H), 7.42 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.5, 27.0, 37.4, 40.9, 48.2, 51.4, 61.0, 165.3, 175.5, 203.7; HRMS calcd for $C_{11}H_{17}NO_6$ 259.1056, found 259.1053.

(*E*)-5-[(*N*-Ethoxycarbonylmethyl)carbamoylmethylidene]-1-methyl-2-pyrrolidinone 31. Compound **30** (65 mg, 0.3 mmol) was treated with methylamine (0.83 mL of a 6 M solution in 1,2-dichloroethane, 20 equiv) as described for **17**. The solvent was removed under reduced pressure, and the

residue was heated (150 °C) at 1 mmHg for 1 h. The residue was purified by radial chromatography (ethyl acetate/dichloromethane, 7:3) to give **31** as a white solid (22 mg, 25%): mp 129−130 °C; IR (KBr) 1738, 1665, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 2.53 (m, 2H), 2.98 (s, 3H), 3.28 (m, 2H), 4.07 (d, J = 4.9 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 5.12 (t, J = 1.7 Hz, 1H) 5.81 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.1, 24.4, 26.9, 28.2, 41.2, 61.5, 93.0, 158.3, 166.6, 170.4, 176.9; HRMS calcd for $C_{11}H_{16}N_2O_4$ 240.1110, found 240.1113.

5-[2-(Ethoxycarbonylmethylamino)-2-oxo-ethyl]-1-methyl-2-pyrrolidinone 32. To a solution of **31** (14 mg, 0.1 mmol) in methanol (5 mL) was added Pd on C (14 mg), and the reaction mixture was stirred vigorously under an atmosphere of hydrogen for 18 h. The mixture was filtered through Celite, and the solvent was removed under reduced pressure to give **32** as an oil (12 mg, 84%): IR (KBr) 1747, 1668 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t J = 7.3 Hz, 3H), 1.74 (m, 2H), 2.22−2.42 (m, 3H), 2.66 (dd J = 5.2 and 14.4 Hz, 1H), 2.80 (s, 3H), 4.00 (m, 1H), 4.03 (d J = 4.9 Hz, 2H), 4.21 (q J = 7.3 Hz, 2H), 6.19 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.1, 24.3, 27.9, 29.6, 40.0, 41.2, 57.1, 61.5, 169.7, 170.0, 175.0; HRMS calcd for $C_{11}H_{18}N_2O_4$ 242.1267, found 242.1264.

(*E*)-1-(2,4-Dimethoxybenzyl)-5-(ethoxycarbonylmethylidene)-2-pyrrolidinone 34. To a solution of **33**[20] (50 mg, 0.2 mmol) in 1,2-dichloroethane (5 mL) was added 2,4-dimethoxybenzylamine hydrochloride (51 mg, 0.3 mmol) and triethylamine (0.34 mL, 0.3 mmol), and the mixture was refluxed for 45 min. The solvent was removed under reduced pressure, and the residue was heated (150−160 °C) at 1 mmHg for 1 h. The resulting oil was purified by radial chromatography (ethyl acetate/petroleum ether, 1:1), and the main fraction was recrystallized (ethyl acetate/petroleum ether) to give **34** (21 mg, 38%): mp 112−113 °C; IR (KBr) 1735, 1618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7.1 Hz), 2.63 (t, J = 7.6 Hz, 2H), 3.25 (t, J = 7.6 Hz, 2H), 3.79 (s, 3H), 3.86 (s, 3H), 4.10 (q, J = 7.0 Hz, 2H), 4.68 (s, 2H), 5.32 (s, 1H), 6.43 (d, J = 8.5 Hz, 1H), 6.45 (s, 1H), 6.95 (d, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 24.6, 28.1, 38.3, 55.3, 59.4, 92.6, 98.44, 104.4, 115.3, 128.7, 157.9, 159.3, 160.4, 167.5, 177.2. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.96; H, 6.70; N, 4.52.

(*Z*)-5-(Ethoxycarbonylmethylidene)-2-pyrrolidinone 35.[17] A solution of cerric ammonium nitrate (255 mg, 0.5 mmol) in water (3 mL) was added dropwise to a solution of **34** (50 mg, 0.2 mmol) in acetone (9 mL) and MeOH (3 mL) at 5 °C. The resulting mixture was stirred for 30 min at 5 °C, and additional cerric ammonium nitrate (255 mg) was added. The mixture was stirred for an additional 1 h at 5 °C and then concentrated under reduced pressure. The residue was extracted with ethyl acetate, and the extract was washed successively with aqueous sodium hydrogen cabonate and brine and then dried. The solution was evaporated to dryness, and the residue was purified by radial chromatography (ethyl acetate/petroleum ether, 1:4) to give **35**[17] (13 mg, 50%) and a fraction containing the corresponding (*E*)-isomer, which was not purified further (3 mg).

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Supporting Information Available: Details of the crystal structure analysis of **24** and ^1H NMR spectra of compounds **14**, **17**, **27**, **28**, and **30**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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