DOI: 10.1002/ejoc.200600153

Amino Acid Esters and Amides for Reductive Amination of Mucochloric Acid: Synthesis of Novel γ-Lactams, Short Peptides and Antiseizure Agent Levetiracetam (Keppra®)

Koushik Das Sarma,[a] Ji Zhang,*[a] Yun Huang,[a] and James G. Davidson[a]

Keywords: Mucochloric acid / Reductive amination / γ-Lactam / Short peptides / Levetiracetam

A simple methodology utilizing mucochloric acid and different α- and β-amino acid esters, amides and short peptides for the synthesis of novel γ-lactam and γ-lactam-based short peptides was developed. The synthesis of an antiseizure agent, Levetiracetam (Keppra®) was demonstrated.

Introduction

The γ-lactam subunit is widespread in nature (Figure 1).[1] This subunit also serves as an important pharmacophore in the drug-discovery process and as a key intermediate in the synthesis of biologically and pharmaceutically useful molecules. For example, compounds **1** and **2** were used to inhibit fatty acid and cholesterol biosynthesis for the treatment of lipoprotein disorders and to inhibit phosphodiesterase IV (PDE-IV), the enzyme linked to allergic and inflammatory diseases, respectively.[2] Other examples include integrin antagonists, chemokine receptor CCR5 antagonists and γ-lactam hydroxamic acids as selective inhibitors of TNF-α converting enzyme.[3] 3,3-Dialkyl- and 3-alkyl-3-benzyl-substituted γ-lactams were reported to show anticonvulsant activity.[4] In addition, the γ-lactam subunit occupies an important place in the discovery of novel HIV protease inhibitors, such as **3**.[5] In the total synthesis of (±)-martinellic acid, a non-peptidic antagonist of bradykinin (BK) B_1 and B_2 receptors, reduction of a γ-lactam to the corresponding amino alcohol is one of the key steps.[6]

Another important role that a γ-lactam plays is to stabilize the N-terminus of peptides against aminoprotease-mediated degradation. In nature, as a pyroglutamoyl group it caps the amino terminus of peptide hormones like gonadotropin-releasing hormone.[7] From a synthesis point of view, this provides a way to synthesize modified peptides of pharmaceutical interest (Figure 2). For instance, piracetam (**4**) was found to have antiepileptic activity.[8] Rolipram (**5**) is an inhibitor of PDE-IV, a cyclic adenosine monophosphate (cAMP) specific phosphodiesterase, and is employed in the treatment of depression.[9] Novel lopinavir analogues incorporating a γ-lactam were synthesized, and the SAR (structure–activity relationships) were explored.[10] The γ-lactam subunit **6** serves as a conformationally rigid scaffold in a polypeptide chain. When incorporated into peptides, a β-turn conformation is stabilized.[11] These are also very useful building blocks for a wide range of peptidic compounds of pharmaceutical interest. For example, γ-lactam-based peptidic inhibitors of the 20S-proteasome (**7**) were identified and a potential plasminogen activator inhibitor **8** was synthesized.[12] Certain spirocyclic γ-lactams were also reported to show pharmaceutical activities.[13]

Recently, we reported a method for preparing α,β-unsaturated γ-butyrolactams by reductive amination of mucochloric acid.[14] The simplicity and efficiency of the methodology prompted us to further use this as a route for synthesizing novel γ-lactam and short peptides. The advantage of using mucochloric (mucobromic) acid is that it is inexpensive, highly functionalized, and the two halogen groups have very different reactivities and thereby offer the possibility of selective functionalization.[15] The γ-butyrolactam can then be easily generated by the reduction of the α,β-unsaturated γ-butyrolactam ring (Scheme 1).

In this paper we report the synthesis of novel γ-lactam and diverse peptides using mucochloric acid as a building block. We further use this simple and efficient methodology to synthesize the antiepileptic drug Keppra®.

[a] Research API, Pfizer Global Research & Development, Ann Arbor Laboratories, Pfizer, Inc.,
2800 Plymouth Road, Ann Arbor, Michigan 48105, USA
Fax: + 1-734-622-3294
E-mail: ji.zhang@pfizer.com
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

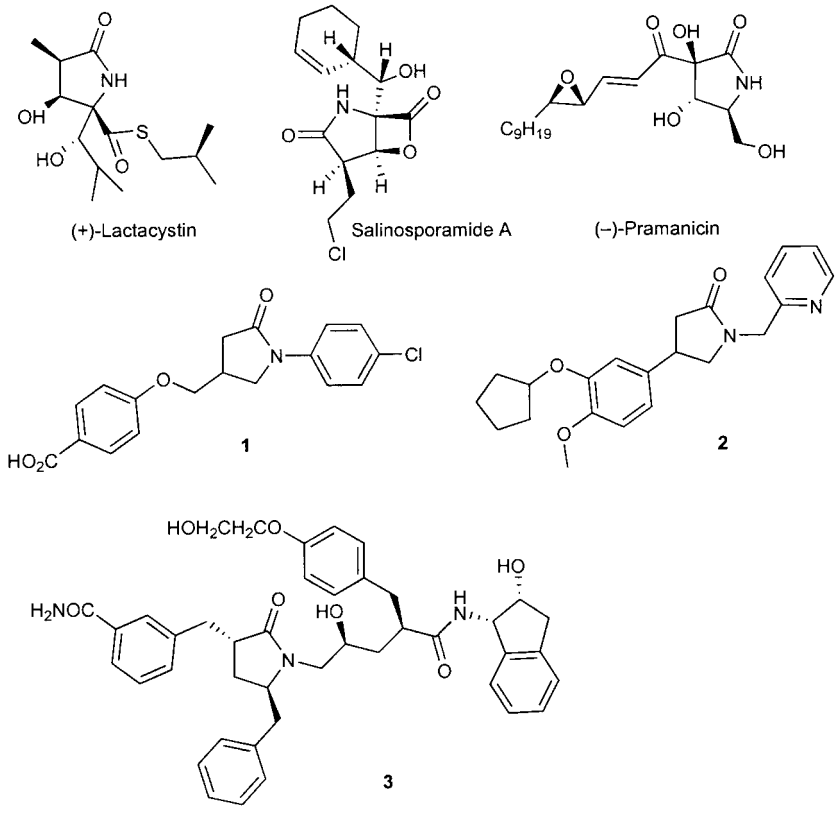


Figure 1. Examples of natural and synthetic γ-lactam derivatives.

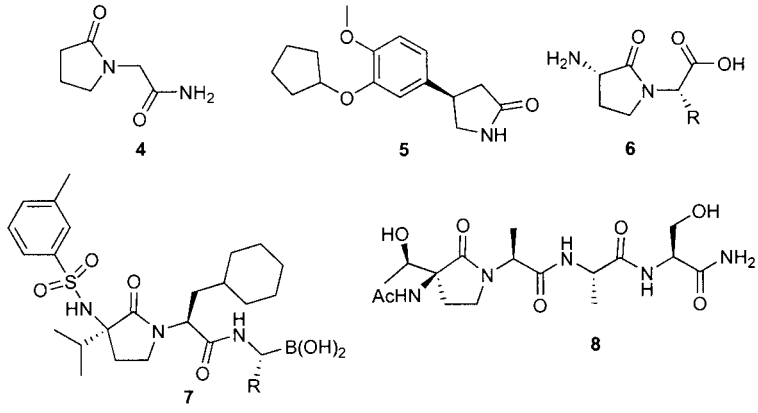
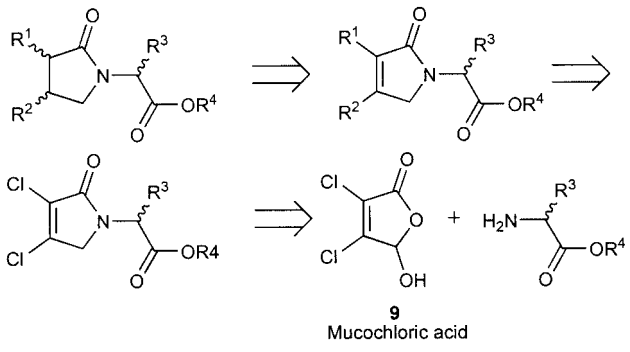


Figure 2. Examples of γ-lactam-containing short peptides.



Scheme 1. Retrosynthetic analysis.

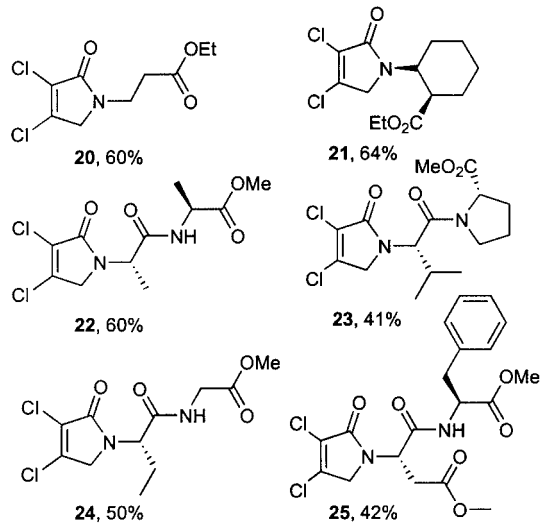
Results and Discussion

Amino Acid Esters and Amides in Reductive Amination of Mucochloric Acid

Reductive amination is an important method to form carbon–nitrogen bonds.[16] Although most primary amines can be utilized for this purpose, the use of amino acids, especially α-amino acids in reductive amination is not very extensive.[17] We initiated our study by the treatment of **9** with the HCl salt of L-alanine ethyl ester (H–Ala–OEt·HCl) using $CHCl_3$ as solvent and $NaBH(OAc)_3$ as the reductive amination reagent. HOAc was found to catalyze this reaction in earlier studies with anilines and other amines.[14] For

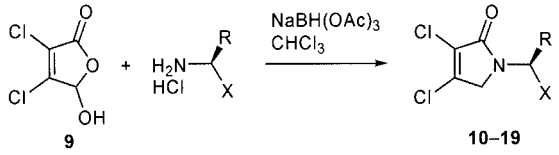
an amine·HCl salt, the addition of NaOAc instead of HOAc was found to provide the same effect. The transformations were found to be slow and 24 h was essential for completion of the reactions. Interestingly, the reaction between **9** and H–Ala–OEt·HCl was found to be complete within 4 h and no catalyst was necessary. After an aqueous workup, the product was isolated in 52% yield. Encouraged by the success, we studied several L-α-amino acid derivatives for their reactivity with **9** using these modified conditions. As seen in Table 1, the reductive amination was successful with a wide range of α-amino acids. The C-terminal protecting group made no difference whatsoever, and the amide group was also well tolerated (Table 1, Entries 9–10). The workup was simple, and a partitioning between $CHCl_3$ and aqueous layers was successful in most of the cases. However, with carboxamide derivatives and some of the esters, the product was found to have partial solubility in the aqueous phase. This was addressed by using a non-aqueous workup employing MeOH to quench the reaction mixture followed by chromatographic purification of the product. Because most commercially available amino acid esters are in their salt form (like HCl salt), this new procedure certainly simplifies the process.

Subsequently, we decided to test the efficacy of this methodology with β-amino acids and dipeptides. As summarized in Scheme 2 the results were very encouraging. The reductive amination with the β-amino acid, β-alanine ethyl ester, proceeded well and after 4 h the product was isolated in 60% yield. Our attempts with several dipeptides were also successful, with reaction completion observed in 4 h in



Scheme 2. Reductive amination with β-amino acids and peptides.

Table 1. Reductive amination with various α-amino acid derivatives.[a]



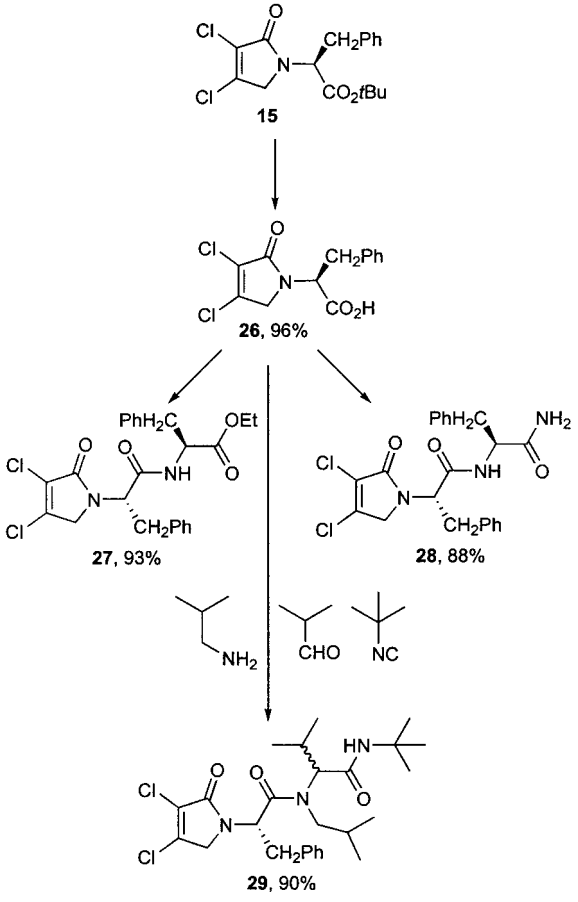
Entry	H_2N–CHR–X·HCl	Product	Yield[b]	Entry	H_2N–CHR–X·HCl	Product	Yield[b]
1	R = Me, X = CO_2Et	**10**	52	6	R = CH_2Ph, X = CO_2tBu	**15**	50
2	R = CH_2Ph, X = CO_2Et	**11**	50	7	R = *i*Bu, X = CO_2tBu	**16**	47
3	R = Et, X = CO_2Me	**12**	56	8	R = *i*Pr, X = CO_2Bn	**17**	50
4	R = CH_2CO_2Me, X = CO_2Me	**13**	41	9	R = CH_2Ph, X = $CONH_2$	**18**	50
5	R = Ph, X = CO_2Me	**14**	50	10	R = *i*Bu, X = $CONH_2$	**19**	45

[a] Reaction conditions: **9**, 1.2 mol-equiv. of the amino acid derivative and 1.5 equiv. of $NaBH(OAc)_3$, 50 mL of $CHCl_3$, stirring at room temp. for 4–6 h. [b] Products were isolated and purified by silica gel chromatography and characterized.

most of the cases. However, to ensure complete conversion, the reactions were worked up after 8 h. Aqueous workup was not successful for the reductive amination with peptides as the products were found to be extremely polar and partially soluble in aqueous medium. Again, non-aqueous workup with MeOH was successful to quench the boron hydride.

Synthesis Novel Short Peptides

With the success of reductive amination with different amino acids and peptide derivatives, we then focused our attention on further utilization of these peptidic building blocks. The *tert*-butyl protecting group of ester **15** can easily be cleaved by CF_3CO_2H/Et_3SiH treatment in CH_2Cl_2. The free acid can then be used as a building block for further synthesis of peptides, another class of pharmacologically important subunits. Thus, treating the free acid **26** with H–Phe–OEt using the standard peptide coupling condition (HOBt/HBTU/DIEA) resulted in the corresponding dipeptide **27** in 93% yield (Scheme 3). Similarly, the dipeptide **28** was synthesized in 88% yield (Scheme 3). Using Ugi-4CC conditions, the short peptide **29** can be synthesized in 90% yield (Scheme 3) by treating **26** with isobutylamine, isobutyraldehyde and *tert*-butyl isocyanide in MeOH. The ease

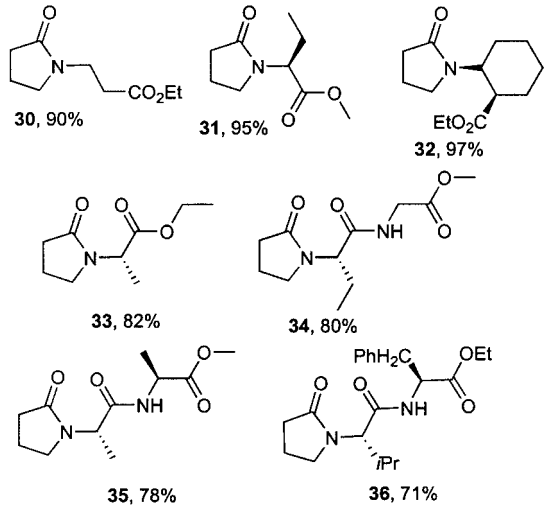


Scheme 3. Application of the reductive amination product in peptide coupling and peptoid synthesis.

of synthesis of **29** provided us with a method to form *N*-alkylated amide bonds, yet another important constituent of modified peptides.[18] *N*-Alkylation increases the lipophilicity of the peptide and induces a conformational change as compared to the parent peptide. In nature, *N*-alkylated amides are found to be incorporated into hormones such as angiotensin and bradykinine to improve their activities.[19] The present methodology offers a unique way of introducing both the γ-lactam and *N*-alkylated amide bond in the same peptide sequence in a rapid and efficient fashion.

Dehalogenation and Synthesis of Keppra®

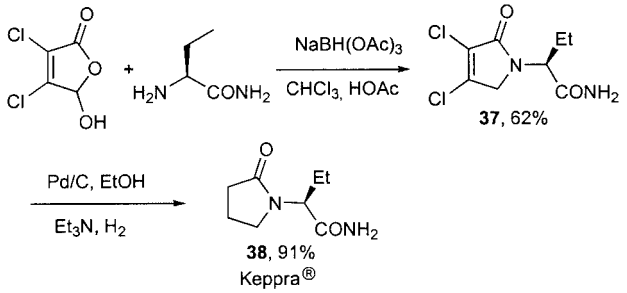
Removing the Cl or Br atom from the mucohalic acid system is critical for further utilization of these useful building blocks. Recently, we have successfully demonstrated a highly efficient method for the reduction.[20] The dehalogenation of these α,β-unsaturated γ-butyrolactams was found to proceed with great ease. With **20** as a substrate, the reaction was found to be complete in 2 h when conducted in EtOH under 345 kPa H_2 in the presence of 10% Pd/C and NEt_3. The dehalogenation was subsequently successfully employed to synthesize several γ-lactam derivatives (Scheme 4). In most of the cases, a simple aqueous workup resulted in a product of sufficiently high purity. Interestingly, the dehalogenation product of **17** is an amino acid with the N-terminus capped by a γ-lactam. This can be used for further construction of polypeptides in solution phase. Using the peptide coupling conditions, the dipeptide **36** was obtained in 71% overall yield (Scheme 4).



Scheme 4. Products from dehalogenation of the α,β-unsaturated γ-lactams.

With the success in reductive amination of mucochloric acid and dehalogenation, we decided to synthesize Levetiracetam (Keppra®, **38**), an antiseizure agent which obtained marketing authorization in the US (2000) and EU (2001).[21] The original synthesis is from (*S*)-2-aminobutyric acid by alkylation of its methyl ester with ethyl 4-bromobutyrate, cyclization and amidation.[22] Under our new ap-

proach, Keppra® was successfully prepared in only two steps, reductive amination of mucochloric acid with amino acid amide, followed by dehalogenation and hydrogenation, with an overall yield of 56% (Scheme 5).



Scheme 5. Synthesis of Keppra® from mucochloric acid.

Conclusions

In this paper, we have reported a simple and efficient two-step synthesis of novel γ-lactam and γ-lactam-based peptides from mucochloric acid. The reductive amination was found to proceed well with α- and β-amino acids as well as with short peptides. These short peptides were found to be versatile building blocks for further synthesis of different peptide derivatives. The resulting α,β-unsaturated γ-lactams could then be reduced to the corresponding γ-lactam-based peptides in high yields. We successfully applied this simple combination of reductive amination and dehalogenation/hydrogenation to synthesize the antiepileptic drug Keppra®. Applications of these peptides as chiral ligands for asymmetric organic synthesis, and results will be reported in due course.

Experimental Section

General: All reactions other than dehalogenations were carried out under nitrogen. All solvents and reagents used were from commercial sources and no further purification was performed. Reactions were monitored by Agilent 1100 series HPLC, mass spectrometry (MS) with a Micromass Platform LC and by thin-layer chromatography on 0.25 mm E. Merck silica gel 60 plates (F_{254}) using UV light and aqueous potassium permanganate/sodium bicarbonate as visualizing agents. E. Merck silica gel 60 (0.040–0.063 mm and 0.063–0.200 mm particle sizes) was used for column chromatography. ^{1}H NMR spectra were recorded at 400 MHz with a Varian UNITY INOVA AS400 instrument. ^{13}C NMR spectra were recorded at 100 MHz with a Varian UNITY Plus INOVA 400 instrument. Elemental analyses were performed out-of-house by Quantitative Technologies Inc.

General Procedure for Reductive Amination: Sodium triacetoxyborohydride (1.5 equiv.) was slowly added to a mixture of mucochloric acid (**9**, 1.7 g, 10.0 mmol) and the amino acid/peptide hydrochloride (1.2 equiv.) in chloroform (50 mL). The reaction mixture was stirred at room temperature for 4–8 h. The reaction mixture was partitioned between water (200 mL) and chloroform (200 mL), the phases were separated and the organic phase was washed once with water (200 mL). The organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography. For water-soluble products, 200 mL of MeOH was added to the reaction mixture after the requisite time and the resulting mixture was stirred for 15 min. The combined organic phases were concentrated under reduced pressure and the crude product was purified by column chromatography.

Ethyl (2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)propanoate (10): Yield 1.3 g, 52%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.98 (m, 1 H), 4.34 (d, J = 18.3 Hz, 1 H), 4.18 (m, 2 H), 4.05 (d, J = 18.3 Hz, 1 H), 1.50 (d, J = 7.6 Hz, 3 H), 1.27 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 164.7, 141.2, 125.3, 61.9, 50.9, 50.0, 15.9, 14.3 ppm. $C_9H_{11}Cl_2NO_3$ (252.09): calcd. C 42.88, H 4.40, Cl 28.13, N 5.56; found C 42.69, H 4.42, Cl 28.23, N 5.48.

Ethyl (2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-3-phenylpropanoate (11): Yield 1.6 g, 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.23 (m, 3 H), 7.19 (m, 2 H), 5.21 (dd, J = 10.3, 5.9 Hz, 1 H), 4.31 (d, J = 18.1 Hz, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 3.93 (d, J = 18.3 Hz, 1 H), 3.40 (dd, J = 14.8, 5.9 Hz, 1 H), 3.07 (dd, J = 14.7, 10.4 Hz, 1 H), 1.25 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 165.0, 141.3, 135.8, 129.1, 128.7, 127.5, 125.2, 62.0, 55.4, 51.6, 36.0, 14.3 ppm. $C_{15}H_{15}Cl_2NO_3$ (328.19): calcd. C 54.90, H 4.61, Cl 21.61, N 4.27; found C 54.74, H 4.50, Cl 21.85, N 4.27.

Methyl (2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)butanoate (12): Yield 1.4 g, 56%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.83 (dd, J = 10.7, 5.3 Hz, 1 H), 4.39 (d, J = 18.3 Hz, 1 H), 4.00 (d, J = 18.3 Hz, 1 H), 3.74 (s, 3 H), 2.08 (m, 1 H), 1.74 (m, 1 H), 0.97 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 165.2, 141.3, 125.3, 55.8, 55.7, 50.9, 23.5, 11.0 ppm. $C_9H_{11}Cl_2NO_3$ (252.09): calcd. C 42.88, H 4.40, Cl 28.13, N 5.56; found C 42.90, H 4.35, Cl 28.03, N 5.43.

Dimethyl (2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-succinate (13): Yield 1.2 g, 41%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.10 (dd, J = 8.2, 4.9 Hz, 1 H), 4.37 (d, J = 18.6 Hz, 1 H), 4.11 (d, J = 18.4 Hz, 1 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 3.05 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 169.6, 164.9, 141.7, 125.1, 53.2, 52.8, 52.6, 51.9, 35.0 ppm. HRMS (ESI): calcd. for $C_{10}H_{12}Cl_2NO_5$ 296.0092 [MH^+], found 296.0085.

Methyl (2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-2-phenylacetate (14): Yield 1.5 g, 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 3 H), 7.27 (m, 2 H), 6.14 (s, 1 H), 4.47 (d, J = 18.5 Hz, 1 H), 3.80 (s, 3 H), 3.59 (d, J = 18.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 164.6, 142.0, 133.5, 129.6, 129.5, 128.7, 124.9, 58.2, 52.9, 51.5 ppm. $C_{13}H_{11}Cl_2NO_3$ (300.14): calcd. C 52.02, H 3.69, Cl 23.62, N 4.67; found C 51.74, H 3.71, Cl 23.55, N 4.48.

***tert*-Butyl (2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-3-phenylpropanoate (15):** Yield 1.8 g, 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (m,3 H), 7.20 (m, 2 H), 5.14 (dd, J = 10.3, 6.2 Hz, 1 H), 4.36 (d, J = 18.8 Hz, 1 H), 3.91 (d, J = 18.2 Hz, 1 H), 3.35 (dd, J = 14.7, 6.1, 1 H), 3.04 (dd, J = 14.7, 10.3 Hz, 1 H), 1.43 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 165.0, 141.2, 136.0, 129.0, 128.7, 127.4, 105.0, 83.1, 55.8, 51.5, 36.2, 28.1 ppm. $C_{17}H_{19}Cl_2NO_3$ (356.24): calcd. C 57.32, H 5.38, Cl 19.90, N 3.93; found C 57.27, H 5.29, Cl 20.04, N 3.83.

***tert*-Butyl (2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-4-methylpentanoate (16):** Yield 1.5 g, 47%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.88 (dd, J = 10.5, 5.5 Hz, 1 H), 4.46 (d, J = 18.4 Hz, 1 H), 3.95 (d, J = 18.6 Hz, 1 H), 1.70 (m, 2 H), 1.49 (m, 1 H), 1.45 (s, 9 H), 0.97 (d, J = 5.3 Hz, 3 H), 0.96 (d, J = 5.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 165.1, 141.2, 125.3, 82.7,

53.3, 51.0, 38.8, 28.2, 25.2, 23.2, 21.4 ppm. $C_{14}H_{21}Cl_2NO_3$ (322.23): calcd. C 52.18, H 6.57, Cl 22.00, N 4.35; found C 52.25, H 6.59, Cl 22.23, N 4.27.

Benzyl (2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-3-methylbutanoate (17): Yield 1.7 g, 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 5 H), 5.20 (d, J = 12.0 Hz, 1 H), 5.14 (d J = 12.0 Hz, 1 H), 4.70 (d, J = 9.9 Hz, 1 H), 4.43 (d, J = 18.9 Hz, 1 H), 4.04 (d, J = 18.7 Hz, 1 H), 2.21 (m, 1 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 165.0, 141.3, 135.2, 128.9, 128.6, 125.1, 67.3, 60.4, 51.4, 29.6, 19.4 ppm. $C_{16}H_{17}Cl_2NO_3$ (342.22): calcd. C 56.15, H 5.01, Cl 20.72, N 4.09; found C 55.95, H 5.02, Cl 20.90, N 4.09.

(2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-3-phenylpropanamide (18): Yield 1.5 g, 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.17 (m, 5 H), 6.33 (br. s, 1 H), 5.57 (br. s, 1 H), 5.00 (m, 1 H), 4.32 (d, J = 18.9 Hz, 1 H), 4.08 (d, J = 18.9 Hz, 1 H), 3.33 (dd, J = 14.2, 7.6 Hz, 1 H), 3.10 (dd, J = 14.2, 8.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 165.2, 141.8, 135.9, 129.1, 128.9, 127.5, 125.0, 56.7, 51.9, 35.5 ppm. LRMS (APCI): m/z = 299.1 [MH^+], 300.1 [$M+2$]H^+.

(2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-4-methylpentanamide (19): Yield 1.2 g, 45%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.50 (br. s, 1 H), 5.66 (br. s, 1 H), 4.84 (dd, J = 8.9, 6.9 Hz, 1 H), 4.40 (d, J = 19.1 Hz, 1 H), 4.04 (d, J = 18.9 Hz, 1 H), 1.74 (m, 2 H), 1.51 (m, 1 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 165.1, 141.7, 125.0, 53.3, 51.3, 38.2, 25.0, 23.0, 22.2 ppm. LRMS (APCI): m/z = 265.1 [MH^+], 267.1 [$M+2$]H^+.

Ethyl 3-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)propanoate (20): Yield 1.5 g, 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (m, 4 H), 3.75 (t, J = 6.2 Hz, 2 H), 2.67 (t, J = 6.2 Hz, 2 H), 1.26 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 164.6, 140.2, 125.6, 61.2, 54.8, 39.3, 33.5, 14.3 ppm. $C_9H_{11}Cl_2NO_3$ (252.09): calcd. C 42.88, H 4.40, Cl 28.13, N 5.56; found C 42.60, H 4.77, Cl 28.00, N 5.47.

Ethyl *cis*-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)cyclohexanecarboxylate (21): Yield 1.9 g, 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.37 (d, J = 19.3 Hz, 1 H), 4.16–3.98 (m, 4 H), 3.18 (m, 1 H), 2.21 (m, 1 H), 2.06 (m, 1 H), 1.86 (m, 1 H), 1.68 (m, 2 H), 1.55 (m, 1 H), 1.37 (m, 2 H), 1.19 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 164.5, 140.7, 125.1, 60.5, 52.8, 52.3, 43.0, 28.4, 25.9, 25.5, 21.5, 14.3 ppm. $C_{13}H_{17}Cl_2NO_3$ (306.18): calcd. C 51.00, H 5.60, Cl 23.16, N 4.57; found C 50.94, H 5.57, Cl 23.42, N 4.47.

Methyl (2*S*)-2-{[(2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)propanoyl]amino}propanoate (22): Yield 1.8 g, 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.69 (br. s, 1 H), 4.87 (q, J = 7.2 Hz, 1 H), 4.49 (q, J = 7.2 Hz, 1 H), 4.41 (d, J = 18.9 Hz, 1 H), 4.11 (d, J = 18.9 Hz, 1 H), 3.75 (s, 3 H), 1.48 (d, J = 7.2 Hz, 3 H), 1.40 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 170.1, 164.9, 141.6, 125.1, 52.7, 51.2, 50.9, 48.5, 18.1, 15.6 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}Cl_2N_2O_4$ 309.0409 [MH^+], found. 309.0414.

Methyl (2*S*)-1-[(2S)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-3-methylbutanoyl]pyrrolidine-2-carboxylate (23): Yield 1.5 g, 41%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.73 (d, J = 11.1 Hz, 1 H), 4.60 (d, J = 19.7 Hz, 1 H), 4.42 (dd, J = 8.6, 5.1 Hz, 1 H), 4.04 (m, 2 H), 3.77 (m, 1 H), 3.74 (s, 3 H), 2.28 (m, 2 H), 2.05 (m, 1 H), 1.99 (m, 2 H), 1.09 (d, J = 6.6 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 168.9, 164.9, 141.6, 124.4, 59.0, 58.4, 52.2, 51.1, 47.5, 29.2, 29.0, 24.8, 19.1, 18.5 ppm. $C_{15}H_{20}Cl_2N_2O_4$ (363.24): calcd. C 46.60, H 5.55, Cl 19.52, N 7.71; found C 49.50, H 5.53, Cl 19.87, N 7.61.

Methyl 2-{[(2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-butanoyl]amino}acetate (24): Yield 1.5 g, 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (br. s, 1 H), 4.68 (dd, J = 8.4, 7.41 Hz, 1 H), 4.40 (d, J = 19.1 Hz, 1 H), 4.05 (d, J = 18.9 Hz, 1 H), 3.99 (d, J = 5.7, 2 H), 3.73 (s, 3 H), 2.04 (m, 1 H), 1.77 (m, 1 H), 0.96 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 170.0, 165.3, 141.7, 124.8, 59.9, 52.6, 51.3, 41.3, 22.8, 10.6 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}Cl_2N_2O_4$ 309.0409 [MH^+], found 309.0449.

Methyl (3*S*)-4-{[(1*S*)-1-Benzyl-2-methoxy-2-oxoethyl]amino}-3-(3,4-dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-4-oxobutanoate (25): Yield 1.9 g, 42%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (m, 3 H), 7.08 (m, 2 H), 6.63 (d, J = 8.6 Hz, 1 H), 5.08 (t, J = 7.6 Hz, 1 H), 4.90 (m, 1 H), 3.86 (d, J = 18.5 Hz, 1 H), 3.78 (s, 3 H), 3.66 (s, 3 H), 3.55 (d, J = 18.5 Hz, 1 H), 3.26 (dd, J = 14.0, 4.7 Hz, 1 H), 2.94 (dd, J = 16.4, 7.4 Hz, 1 H), 2.87 (dd, J = 14.1, 9.5 Hz, 1 H), 2.67 (dd, J = 16.3, 7.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 170.3, 167.8, 164.7, 141.8, 136.0, 129.2, 128.7, 127.2, 125.0, 53.0, 52.8, 52.5, 52.0, 51.1, 38.3, 33.7 ppm. $C_{19}H_{20}Cl_2N_2O_6$ (443.28): calcd. C 51.48, H 4.55, Cl 16.00, N 6.32; found C 51.45, H 4.52, Cl 16.30, N 6.24.

(2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-3-phenylpropanoic Acid (26): TFA (15 mL, 93.9 mmol) was added to a solution of **19** (3.3 g, 9.3 mmol) and Et_3SiH (1.6 mL, 10.0 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was stirred at room temperature for 3.5 h after which the volatilities were removed under high vacuum. The resulting white solid was dried in a vacuum oven at ca. 40 °C overnight to yield 2.7 g (96%) of the desired product. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.30–7.19 (m, 5 H), 4.93 (dd, J = 11.1, 8.9 Hz, 1 H), 4.33 (d, J = 20.0 Hz, 1 H), 4.24 (d, J = 20.0 Hz, 1 H), 3.30 (dd, J = 14.4, 4.9 Hz, 1 H), 3.13 (dd, J = 14.4, 11.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 171.2, 163.7, 141.7, 137.1, 128.6, 126.6, 123.3, 55.9, 51.5, 34.4 ppm. $C_{13}H_{11}Cl_2NO_3$ (300.14): calcd. C 52.02, H 3.69, Cl 23.62, N 4.67; found C 51.90, H 3.53, Cl 23.35, N 4.59.

General Procedure for Peptide Coupling (Scheme 3): Equimolar amounts of all the reactants were stirred in CH_2Cl_2 (10 mL for a 1.3 mmol scale) at room temperature for 5 min followed by dropwise addition of DIEA. The reaction mixture was stirred overnight, and the solvent was removed under high vacuum. The crude product was purified by column chromatography (SiO_2, 25–60% ethyl acetate in hexanes) to yield the desired product.

Ethyl (2*S*)-2-{[(2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-3-phenylpropanoyl]amino}-3-phenylpropanoate (27): Yield 0.6 g, 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.19 (m, 6 H), 7.15 (m, 2 H), 7.06 (m, 2 H), 6.38 (br. d, J = 8.6 Hz, 1 H), 4.92 (dd, J = 8.9, 7.3 Hz, 1 H), 4.85 (m, 1 H), 4.18 (q, J = 8.0 Hz, 2 H), 3.84 (d, J = 16.0 Hz, 1 H), 3.68 (d, J = 20.0 Hz, 1 H), 3.25–3.19 (m, 2 H), 2.96 (dd, J = 14.5, 8.9 Hz, 1 H), 2.84 (dd, J = 14.0, 9.0 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 168.3, 164.8, 141.5, 135.9, 135.8, 129.3, 129.0, 128.8, 128.6, 127.3, 127.2, 125.0, 61.9, 56.2, 53.0, 51.1, 38.5, 34.8, 14.3 ppm. $C_{24}H_{24}Cl_2N_2O_4$ (475.36): calcd. C 60.64, H 5.09, Cl 14.92, N 5.89; found C 60.38, H 4.97; Cl, 14.96, N 5.82.

(2*S*)-2-{[(2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-3-phenylpropanoyl]amino}-3-phenylpropanamide (28): Yield 0.5 g, 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.14 (m, 10 H), 6.93 (d, J = 8.6 Hz, 1 H), 5.67 (br. s, 1 H), 5.55 (br. s, 1 H), 4.96 (t, J = 8.1 Hz, 1 H), 4.73 (m, 1 H), 3.91 (d, J = 18.9 Hz, 1 H), 3.67 (d,

J = 18.9 Hz, 1 H), 3.21 (m, 1 H), 2.96–2.85 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 168.8, 164.8, 141.7, 136.6, 135.9, 129.3, 129.1, 128.7, 127.5, 127.1, 124.8, 56.6, 53.9, 51.4, 37.9, 35.4 ppm. HRMS (ESI): calcd. for $C_{22}H_{21}Cl_2N_3NaO_3$ 468.0858 [M + Na$^+$], found 468.0868.

***N*-*tert*-Butyl-2-{[(2*S*)-2-(3,4-dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)-3-phenylpropanoyl](2-methylpropyl)amino}-3-methylbutanamide (29, diastereomeric mixture):** (2-Methylpropyl)amine (0.18 mL, 1.9 mmol) was added dropwise to a solution of isobutyraldehyde (0.17 mL, 1.9 mmol) in MeOH (5 mL). The resulting mixture was stirred at room temperature for 45 min followed by the addition of **26** [0.5 g, 1.7 mmol; as a solution in MeOH (5 mL)] and *tert*-butyl isocyanide (0.19 mL, 1.7 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed under high vacuum and the crude product was purified by column chromatography (SiO_2, 15–50% ethyl acetate in hexanes) to yield 0.8 g (90%) of the product. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.07 (m, 5 H), 5.65 and 5.53 (m, 1 H), 4.43–4.05 (m, 2 H), 3.58 (m, 1 H), 3.44–2.72 (m, 4 H), 1.30, 1.29 and 1.27 (s, 9 H), 0.91–0.44 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 172.3, 171.4, 164.4, 141.8, 135.5, 129.3, 129.1, 127.7, 124.8, 70.0, 67.7, 67.0, 53.6, 53.3, 51.8, 51.4, 36.7, 28.5, 28.4, 27.8, 27.5, 27.3, 20.1, 19.8, 19.4, 19.3, 19.1 ppm. HRMS (ESI): calcd. for $C_{26}H_{38}Cl_2N_3O_3$ 510.23 [MH$^+$], found 510.23.

General Procedure for Dehalogenation: The reductive amination product (4.0 mmol) was hydrogenated at 345 kPa in the presence of 10% Pd/C (0.1 g) and triethylamine (2.5 equiv.) in EtOH (45 mL) for 2 h. The filtered reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, ethyl acetate/hexanes).

Ethyl 3-(2-Oxopyrrolidin-1-yl)propanoate (30): Yield 0.7 g, 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12 (q, J = 7.2 Hz, 2 H), 3.56 (t, J = 6.8 Hz, 2 H), 3.40 (t, J = 8.0 Hz, 2 H), 2.54 (m, 2 H), 2.34 (t, J = 8.1 Hz, 2 H), 2.00 (m, 2 H), 1.24 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 171.9, 60.9, 47.9, 38.8, 32.9, 31.1, 18.3, 14.4 ppm. HRMS (ESI): calcd. for $C_9H_{16}NO_3$ 186.1130 [MH$^+$], found 186.1133.

Methyl (2*S*)-2-(2-Oxopyrrolidin-1-yl)butanoate (31): Yield 0.7 g, 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.69 (m, 1 H), 3.70 (s, 3 H), 3.50 (m, 1 H), 3.33 (m, 1 H), 2.43 (m, 2 H), 2.03 (m, 3 H), 1.68 (m, 1 H), 0.91 (t, J = 8.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 171.6, 55.1, 52.1, 43.5, 30.8, 22.1, 18.2, 10.7 ppm. $C_9H_{15}NO_3$ (185.22): calcd. C 58.36, H 8.16, N 7.56; found C 58.06, H 8.25, N 7.54. $[\alpha]_D^{20}$ = –52.24 (c = 1, MeOH).

Ethyl *cis*-2-(2-Oxopyrrolidin-1-yl)cyclohexanecarboxylate (32): Yield 0.9 g, 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15–4.02 (m, 3 H), 3.52 (m, 1 H), 3.40 (m, 1 H), 3.07 (m, 1 H), 2.35 (t, J = 8.0 Hz, 2 H), 2.17 (m, 1 H), 1.95 (m, 2 H), 1.86 (m, 2 H), 1.70 (m, 1 H), 1.61 (m, 1 H), 1.53 (m, 2 H), 1.40 (m, 1 H), 1.25 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 174.2, 60.1, 51.8, 45.1, 45.5, 31.4, 28.1, 25.6, 25.3, 21.2, 18.7, 14.2 ppm. HRMS (ESI): calcd. for $C_{13}H_{22}NO_3$ 240.1599 [MH$^+$], found 240.1601.

Ethyl (2*S*)-2-(2-Oxopyrrolidin-1-yl)propanoate (33): Yield 0.6 g, 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.85 (q, J = 7.41 Hz, 1 H), 4.16 (m, 2 H), 3.49 (m, 1 H), 3.39 (m, 1 H), 2.41 (m, 2 H), 2.05 (m, 2 H), 1.40 (d, J = 7.41 Hz, 3 H), 1.25 (t, J = 7.12 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 171.7, 61.4, 49.5, 43.7, 31.1, 18.4, 15.0, 14.4 ppm. HRMS (ESI): calcd. for $C_9H_{16}NO_3$ 186.1130 [MH$^+$], found 186.1129. $[\alpha]_D^{20}$ = –40.00 (c = 1, MeOH).

Methyl 2-{[(2*S*)-2-(2-Oxopyrrolidin-1-yl)butanoyl]amino}acetate (34): Yield 0.8 g, 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.66 (br. s, 1 H), 4.50 (dd, J = 8.8, 6.8 Hz, 1 H), 4.11 (dd, J = 18.1, 6.4 Hz, 1 H), 3.88 (dd, J = 18.0, 5.2 Hz, 1 H), 3.74 (s, 3 H), 3.41 (m, 2 H), 2.46 (m, 2 H), 2.12–1.96 (m, 3 H), 1.71 (m, 1 H), 0.92 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 170.4, 170.2, 56.5, 52.5, 44.0, 41.1, 31.3, 21.0, 18.4, 10.7 ppm. $C_{11}H_{18}N_2O_4$ (242.27): calcd. C 54.53, H 7.49, N 11.56; found C 54.90, H 7.66, N 11.28. $[\alpha]_D^{20}$ –96.54 (c = 1, MeOH).

Methyl (2*S*)-2-{[(2*S*)-2-(2-Oxopyrrolidin-1-yl)propanoyl]amino}-propanoate (35): Yield 0.8 g, 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.62 (br. S, 1 H), 4.72 (q, J = 7.2 Hz, 1 H), 4.50 (m, 1 H), 3.75 (s, 3 H), 3.44 (m, 2 H), 2.43 (m, 2 H), 2.05 (m, 2 H), 1.39 (d, J = 7.2 Hz, 3 H), 1.38 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8, 173.2, 170.5, 52.7, 50.4, 48.3, 43.9, 31.3, 18.4 (2 C), 14.0 ppm. $C_{11}H_{18}N_2O_4$ (242.27): calcd. C 54.53, H 7.49, N 11.56; found C 54.53, H 7.53, N 11.32. $[\alpha]_D^{20}$ = –89.11 (c = 1, MeOH).

Ethyl (2*S*)-2-{[(2*S*)-3-Methyl-2-(2-oxopyrrolidin-1-yl)butanoyl]-amino}-3-phenylpropanoate (36): Yield 1.0 g, 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (m, 3 H), 7.15 (m, 2 H), 6.45 (br. d, J = 7.8 Hz, 1 H), 4.87 (m, 1 H), 4.18 (q, J = 7.2 Hz, 2 H), 4.00 (d, J = 11.1 Hz, 1 H), 3.27 (m, 1 H), 3.19 (dd, J = 14.0, 5.3 Hz, 1 H), 3.10 (m, 1 H), 2.94 (dd, J = 14.0, 8.6 Hz, 1 H), 2.37 (m, 1 H), 2.22 (m, 2 H), 1.87 (m, 2 H), 1.25 (t, J = 7.2 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.81 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8, 171.3, 169.1, 136.3, 129.4, 128.7, 127.2, 62.1, 61.7, 52.3, 44.3, 38.3, 31.1, 26.3, 19.6, 18.8, 18.3, 14.3 ppm. $C_{20}H_{28}N_2O_4$ (360.45): calcd. C 66.64, H 7.83, N 7.77; found C 66.29, H 8.07, N 7.68. $[\alpha]_D^{20}$ = –119.84 (c = 1, MeOH).

(2*S*)-2-(3,4-Dichloro-2,5-dihydro-2-oxo-1*H*-pyrrol-1-yl)butanamide (37): Sodium triacetoxyborohydride (6.3 g, 30.0 mmol) was slowly added to a mixture of mucochloric acid (**9**, 3.4 g, 20.0 mmol), (2*S*)-2-aminobutanamide (2.1 g, 20 mmol) and HOAc (2 mL) in chloroform (100 mL). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was partitioned between a saturated solution of NH_4Cl (200 mL) and chloroform (300 mL), the phases were separated and the organic phase was washed with water (200 mL) and brine (100 mL). The organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to yield 2.9 g (62%) of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45 (br. s, 1 H), 5.67 (br. s, 1 H), 4.65 (dd, J = 8.6, 7.0 Hz, 1 H), 4.40 (d, J = 19.1 Hz, 1 H), 4.07 (d, J = 19.1 Hz, 1 H), 2.02 (m, 1 H), 1.78 (m, 1 H), 0.96 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 165.1, 141.5, 124.8, 56.5, 51.1, 22.6, 10.5 ppm. $C_8H_{10}Cl_2N_2O_2$ (237.08): calcd. C 40.53, H 4.25, N 11.82; found C 40.69, H 4.31, N 11.68.

(2*S*)-2-(2-Oxopyrrolidin-1-yl)butanamide (38):[23] The reduction was carried out on a 11.0-mmol scale to yield 1.6 g (91%) of the product. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.49 (br. s, 1 H), 5.78 (br. s, 1 H), 4.47 (dd, J = 8.8, 6.8 Hz, 1 H), 3.42 (m, 2 H), 2.42 (m, 2 H), 2.04 (m, 2 H), 1.95 (m, 1 H), 1.69 (m, 1 H), 1.34 (t, J = 7.2 Hz, 1 H), 0.90 (t, J = 7.4 Hz, 3 H) ppm.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectroscopic data of the compounds.

Acknowledgments

We thank Dr. Peter Green for encouraging and supporting science and technology innovation in the Michigan Laboratories. We ap-

preciate Mr. Mark Lovodahl's assistance with the hydrogenation, and K. D. S. wishes to thank Pfizer, Inc. for a postdoctoral fellowship.

[1] a) E. J. Corey, W.-D. Z. Li, *Chem. Pharm. Bull.* **1999**, *47*, 1–10; b) C. E. Masse, A. J. Morgan, J. Adams, J. S. Panek, *Eur. J. Org. Chem.* **2000**, 2513–2528; c) R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, *Angew. Chem. Int. Ed.* **2003**, *42*, 355–357; d) A. G. M. Barrett, J. Head, M. L. Smith, N. S. Stock, A. J. P. White, D. J. Williams, *J. Org. Chem.* **1999**, *64*, 6005–6018; e) P. W. Sorensen, J. M. Fine, V. Dvornikovs, C. S. Jeffrey, F. Shao, J. Wang, L. A. Vrieze, K. R. Anderson, T. R. Hoye, *Nat. Chem. Biol.* **2005**, *1*, 324–328.

[2] a) S. Fuji, H. Kawamura, S. Watanabe, Eur. Pat. Appl. No. EP 0393607 A2 19901024, **1990**; b) P. E. Bender, S. B. Christensen IV, PCP Int. Appl. No. WO 9307141 A1 19921002, **1992**.

[3] a) C. Dominguez, G. Chen, N. Xi, S. Xu, N. Han, Q. Liu, Q. Huang, A. Siegmund, M. Handley, L. Liu, A. S. Kiselyov, PCP Int. Appl. WO 0144230 A1 20010621, **2001**; b) Y. Ishihara, S. Imamura, S. Hashiguchi, O. Nishimura, N. Kanzaki, M. Baba, Eur. Pat. Appl. No. EP 1180513 A1 20020220, **2002**; c) J. J.-W. Duan, L. Chen, Z. R. Wasserman, Z. Lu, R.-Q. Liu, M. B. Covington, M. Qian, K. D. Hardman, R. L. Magolda, R. C. Newton, D. D. Christ, R. R. Wexler, C. P. Decicco, *J. Med. Chem.* **2002**, *45*, 4954–4957.

[4] P. A. Reddy, B. C. H. Hsiang, T. N. Latifi, M. W. Hill, K. E. Woodward, S. M. Rothman, J. A. Ferrendelli, D. F. Covey, *J. Med. Chem.* **1996**, *39*, 1898–1906.

[5] a) W. M. Kazmierski, W. Andrews, E. Furfine, A. Spaltenstein, L. Wright, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5689–5692; b) A. Spaltenstein, M. R. Almond, W. J. Bock, D. G. Cleary, E. S. Furfine, R. J. Hazen, W. M. Kazmierski, F. G. Salituro, R. D. Tung, L. L. Wright, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1159–1162; c) F. G. Salituro, C. T. Baker, J. J. Court, D. D. Deininger, E. E. Kim, B. Li, P. M. Novak, B. G. Rao, S. Pazhanisamy, M. D. Porter, W. C. Schairer, R. D. Tung, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3637–3642.

[6] B. B. Snider, Y. Ahn, S. M. O'Hare, *Org. Lett.* **2001**, *3*, 4217–4220.

[7] B. L. Currie, H. Sievertsson, C. Bogentoft, J. K. Chang, K. Folkers, C. Y. Bowers, R. F. Doolittle, *Biochem. Biophys. Res. Commun.* **1971**, *42*, 1180–1184.

[8] S. Shorvon, *Lancet* **2001**, *358*, 1885–1892.

[9] a) G. M. Rose, A. Hopper, M. De Vivo, A. Tehim, *Curr. Pharm. Des.* **2005**, *11*, 3329–3334; b) J. Zhu, E. Mix, B. Winbald, *CNS Drug Rev.* **2001**, *7*, 387–398; c) D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, J. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13097–13105.

[10] H. L. Sham, D. A. Betebenner, W. Rosenbrook, T. Herrin, A. Saldivar, S. Vasavanonda, J. L. Plattner, D. W. Norbeck, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2643–2645.

[11] a) R. M. Freidinger, D. S. Perlow, D. F. Veber, *J. Org. Chem.* **1982**, *47*, 104–109; b) I. M. Bell, S. N. Gallicchio, M. Abrams, D. C. Beshore, C. A. Buser, J. C. Culberson, J. Davide, M. Ellis-Hutchings, C. Fernandes, J. B. Gibbs, S. L. Graham, G. D. Hartman, D. C. Heimbrook, C. F. Homnick, J. R. Huff, K. Kassahun, K. S. Koblan, N. E. Kohl, R. B. Lobell, J. J. Lynch Jr, P. A. Miller, C. A. Omer, A. D. Rodrigues, E. S. Wash, T. M. Williams, *J. Med. Chem.* **2001**, *44*, 2933–2949.

[12] a) A. V. Purandare, H. Wan, N. Laing, K. Benbatoul, W. Vaccaro, M. A. Poss, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4701–4704; b) P. R. Guzzo, M. P. Trova, T. Inghardt, M. Linschoten, *Tetrahedron Lett.* **2002**, *43*, 41–43.

[13] a) Y. Auberson, R. Glatthar, R. Salter, O. Simic, M. Tintelnot-Blomley, PCT Int. Appl. No. WO2005035535 A1 20050421, **2005**; b) C. P. Decicco, A. J. Tebben, L. A. Thompson, A. P. Combs, PCT Int. Appl. No. WO2004013098 A1 20040212, **2004**; c) H. Bittermann, J. Einsiedel, H. Hübner, P. Gmeiner, *J. Med. Chem.* **2004**, *47*, 5587–5590.

[14] J. Zhang, P. G. Blazecka, J. G. Davidson, *Org. Lett.* **2003**, *5*, 553–556.

[15] a) P. G. Blazecka, D. Belmont, T. Curran, D. Pflum, J. Zhang, *Org. Lett.* **2003**, *5*, 5015–5017; b) J. Zhang, P. G. Blazecka, D. Belmont, J. G. Davidson, *Org. Lett.* **2002**, *4*, 4559–4561.

[16] a) A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849–3862; b) A. F. Abdel-Magid, C. A. Maryanoff, K. G. Carson, *Tetrahedron Lett.* **1990**, *31*, 5595–5598; c) V. I. Tararov, A. Börner, *Synlett* **2005**, 203–211; d) E. W. Baxter, A. B. Reitz, *Org. React.* **2002**, *59*, 1–714.

[17] a) D. M. Fitch, K. A. Evans, D. Chai, K. J. Duffy, *Org. Lett.* **2005**, *7*, 5521–5524; b) K. N. White, J. P. Konopelski, *Org. Lett.* **2005**, *7*, 4111–4112; c) D. C. Beshore, C. J. Dinsmore, *Org. Lett.* **2002**, *4*, 1201–1204; d) J. Cluzeau, W. D. Lubell, *J. Org. Chem.* **2004**, *69*, 1504–1512; e) X.-H. Jiang, Y.-L. Song, D.-Z. Feng, Y.-Q. Long, *Tetrahedron* **2005**, *61*, 1281–1288; f) E. Dietrich, W. D. Lubell, *J. Org. Chem.* **2003**, *68*, 6988–6996; g) S. Tchertchian, O. Hartley, P. Botti, *J. Org. Chem.* **2004**, *69*, 9208–9214; h) S. Xiao, Y. Li, Y. Li, H. Liu, H. Li, J. Zhuang, Y. Liu, F. Lu, D. Zhanga, D. Zhu, *Tetrahedron Lett.* **2004**, *45*, 3975–3978.

[18] N. Venkatesan, B. H. Kim, *Curr. Med. Chem.* **2002**, *9*, 2243–2270.

[19] a) J. Gante, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699–1720; b) D. Roemer, H. H. Buescher, R. C. Hill, J. Pless, W. Bauer, F. Cardinaux, A. Closse, D. Hauser, R. Huguenin, *Nature* **1977**, *268*, 547–549; c) C. Rivier, J. Rivier, W. Vale, *Science* **1980**, *210*, 93–95; d) B. E. B. Sandberg, C. Lee, M. R. Hanley, L. L. Iversen, *Eur. J. Biochem.* **1981**, *114*, 315–327.

[20] J. Zhang, P. G. Blazecka, H. Berven, D. Belmont, *Tetrahedron Lett.* **2003**, *44*, 5579–5582.

[21] a) R. Grant, S. D. Shorvon, *Epilepsy Res.* **2000**, *42*, 89–95; b) S. D. Shorvon, A. Löwenthal, D. Janz, E. Bielen, P. Loiseau, *Epilepsia* **2000**, *41*, 1179–1186.

[22] a) C. Ates, J. Surtees, A.-C. Burteau, V. Marmon, E. Cavoy, PCT Int. Appl. No. WO2003014080 A2 20030220, **2003**; b) J. Surtees, F. Lurquin, O. Diouf, PCT Int. Appl. No. WO2005028435 A1 20050331, **2005**.

[23] A. H. Gouliaev, J. B. Monster, M. Vedso, A. Senning, *Org. Prep. Proced. Int.* **1995**, *27*, 273–303.

Received: February 22, 2006
Published Online: June 12, 2006

