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Ring-deactivated Hydroxymethylpyrroles as Inhibitors of α-Chymotrypsin

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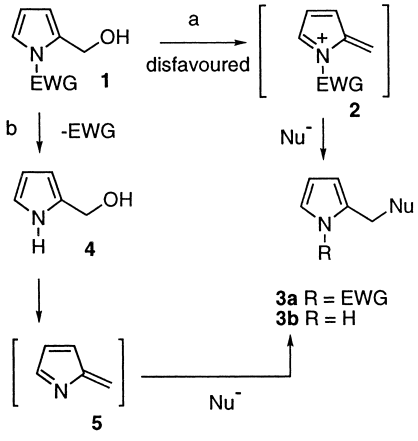
Abstract—*N*-Acyl and *N*-sulfonylhydroxymetyhylpyrroles have been synthesised and shown to inhibit α-chymotrypsin. A hydrophobic group in the *N*-substituent has been shown to be required for activity.

Introduction

We have an ongoing interest in the design of inhibitors of serine proteases based on simple heterocycles that possess well-defined chemical reactivity. To this end we reported that substitution of a hydroxymethylpyrrole with an electron withdrawing group (EWG) on nitrogen, as in depicted in **1**, results in deactivation of the pyrrole ring and hence modulation of its chemical reactivity.[1] The net result is suppression of azafulvenium **2** formation, and hence its subsequent reactions. We also demonstrated that hydrolytic removal of the EWG from these pyrroles (route b, Scheme 1) unmasks the latent reactivity to allow formation of a highly electrophilic azafulvene **5**. This species then reacts readily with an available nucleophile to give **3b**.[2] A sequence of reactions of this type (i.e., the conversion of **4** to **3b**, via **5**) is central to a number of synthetic methods[3,4] and also to the biosynthesis of porphyrins and corrins.[5] Given this well-defined chemistry, we postulate that reaction sequence b (Scheme 1) would form the basis of an inhibitor of serine proteases[6] if the enzyme were able to catalyse removal of the EWG (e.g. deacylation) via its normal catalytic action. The resulting hydroxymethylpyrrole would yield an azafulvene capable of inhibiting the enzyme via covalent attachment (cf. conversion of **5** into **3a** where Nu^- is the enzyme). Figure 1 shows the relationship between a natural substrate of a serine protease (the site of hydrolysis is shown by an arrow) and the proposed inhibitors. In this paper, we report the synthesis of some ring-deactivated hydroxymethylpyrroles and the initial results of the screening of these compounds against α-chymotrypsin using a simple 96-well plate inhibitory assay.



Scheme 1.

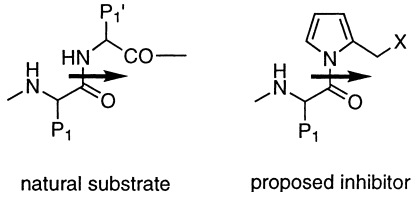


Figure 1.

Results and Discussion

We reasoned that the EWG group in **1** would need to mimic the P_1 substituent of a natural peptidic substrate of the target serine protease (e.g., α-chymotrypsin) in order

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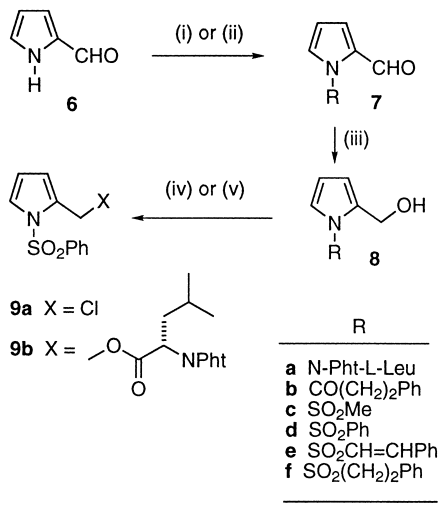
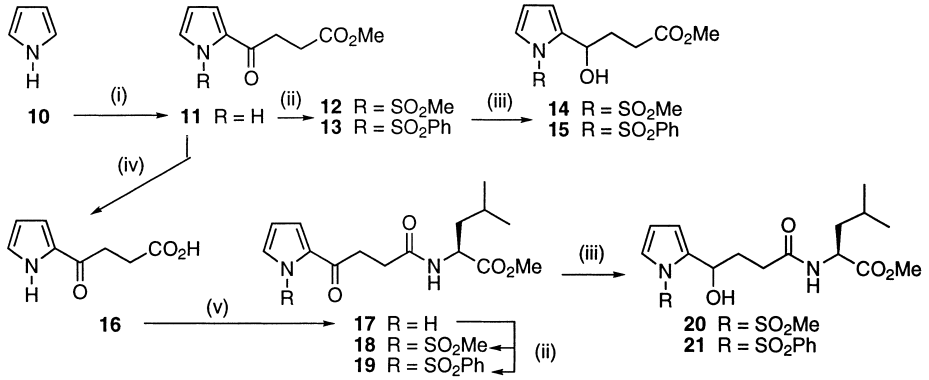


Scheme 2. Reagents and conditions: (i) NaH then either *N*-Pht-L-Leu-F (87%) or $MeSO_2Cl$ (93%) or $PhSO_2Cl$ (97%) or $PhCH{:}CHSO_2Cl$ (56%) or $Ph(CH_2)_2SO_2Cl$ (84%); (ii) DMAP, DIPEA, CH_2Cl_2 then $Ph(CH_2)_2COCl$ (79%); (iii) $Zn(BH_4)_2$, Et_2O, 0 °C (88–94%); (iv) DIPEA, $MeSO_2Cl$ then 10% aq HCl (**9a**, quant); (v) DMAP, DIPEA, *N*-Pht-L-Leu-F, CH_2Cl_2 (**9b**, 90%).

to obtain an effective inhibitor of the enzyme (see Fig. 1).[7] Only then would it bind effectively to the enzyme. With this in mind we initially prepared derivative **8a**[8] in which the *N*-acyl group is an amino acid (Scheme 2). A number of other *N*-substituted ring-deactivated hydroxymethylpyrroles (**8b–f**, **14**, **15**, **20**, **21** and **27**)[9] were then prepared in order to establish which *N*-substituents provide inhibitors of α-chymotrypsin (Schemes 2–4). We then carried out some preliminary studies on modifying the leaving group (see structures **9**, Scheme 2).

The target derivatives were prepared as detailed in Schemes 2–4. Treatment of 2-formylpyrrole **6** with sodium hydride followed by the addition of either *N*-phthalyl-L-leucine acid fluoride[10] or the respective sulfonyl chlorides gave compounds **7a**,**c–f** in good yields. Compound **7b** was prepared under milder conditions using 4-dimethylaminopyridine (DMAP) and *N*,*N*-diisopropylethylamine (DIPEA) as the coupling agents. The *N*-protected 2-formylpyrroles were then simply reduced to the desired hydroxymethylpyrroles **8** using zinc borohydride. Compounds **9** were conveniently prepared from **8d** (Scheme 2). Treatment of **8d** with mesyl chloride in the presence of DIPEA gave **9a** while an analogous reaction using *N*-phthalyl-L-leucine acid fluoride and DIPEA/DMAP gave **9b**.

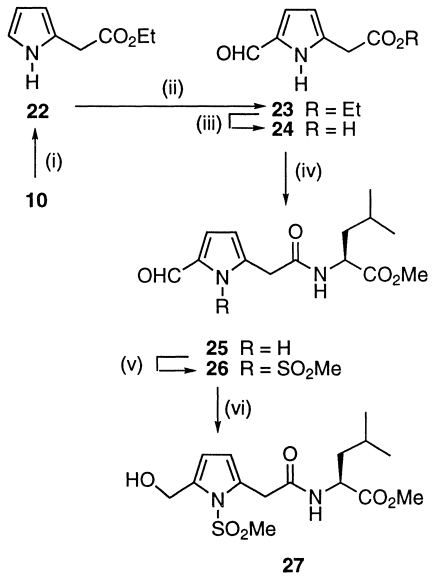
The side-chain modified derivatives **14**, **15**, **20**, **21** and **27** were prepared as detailed in Schemes 3 and 4. The extended side chain of **14**, **15**, **20** and **21** was introduced by acylating the Grignard derivative of pyrrole **10** with methyl succinyl chloride to give the key derivative **11** (Scheme 3). Direct sulfonylation of **11** then gave **12** and **13** that yielded the desired hydroxymethylpyrroles **14** and **15**, respectively, on reduction of the ketone with sodium borohydride. The methyl ester of **11** was also hydrolysed and the corresponding acid **16** was coupled with the methyl ester of L-leucine using standard peptide coupling conditions, to give **17**. Sulfonylation of **17**, followed by reduction, gave **20** and **21** as mixtures of epimers. In the last series of reactions, the Grignard derivative of pyrrole **10** was reacted with ethyl bromoactetate to give **22** (Scheme 4). Compound **22** was then α-formylated to give **23**, the ester of which was hydrolyzed. The resulting free acid **24** was then coupled to L-leucine methyl ester to give **25** which was *N*-mesylated to give **26**. The desired compound **27** was finally prepared by reduction of the formyl group of **26** using zinc borohydride. Compounds **8a–f**, **14**, **15**, **20**, **21** and **27** were assayed against α-chymotrypsin using a simple and convenient 96-well-based assay system. We were interested in a rapid screening of activity and as such inhibition data was conveniently determined at two concentrations, that is, 12.5 and 125 μg/mL (see Table 1). With the exception of **8c**, all the simple *N*-acyl and *N*-sulfonyl hydroxymethylpyrrole derivatives of type **8** inhibited α-chymotrypsin. The most potent compound inhibited α-chymotrypsin to the extent of 20% at 12.5 μg/mL (53 μM). Of particular interest is the fact that inhibitory activities of the *N*-sulfonyl derivatives (**8d–f**) are similar to the *N*-acyl derivatives (**8a–b**), at



Scheme 3. Reagents and conditions: (i) MeMgI, Et_2O, reflux then $MeO_2C(CH_2)_2COCl$, reflux (49%); (ii) NaH, THF then either Me_sO_2Cl (**12**, 86%: 18, 50%) or $PhSO_2Cl$ (**13**, 43%); (iii) $NaBH_4$, MeOH, 0 °C (**14**, 85%), (**15**, 90%), (**20**, 89%), (**21**, 89% for two steps); (iv) NaOH, MeOH–H_2O (**16**, 78%); (v) L-LeuOMe.HCl, EDCI, HOBt, DIPEA (93%).

both concentrations studied. The inactivity of **8c** supports the notion[11] that a large hydrophobic group is required on nitrogen to promote binding to α-chymotrypsin—this group would correspond to the P_1 residue[1] of the natural substrate of α-chymotrypsin (see Fig. 1).

Having established that an *N*-phenylsulfonyl group (as in **8d**) provides active compounds, we turned our attention to determining which group at the 2-methyl position was optimal for enzyme inhibition. The results for **9a** and **9b** show that chloro and *N*-phthalyl-L-leucinyl groups are less favored for enzyme inhibition than the hydroxyl group of **8**. This suggests that potency is not simply enhanced by an increase in leaving group ability of this substituent (cf. **9a** and **8d** in Table 1) or its ability to mimic a natural peptidic substrate of the enzyme (see **9b**).[5] The last series of compounds tested, namely **14**, **15**, **20**, **21** and **27** show that there is little gain in extending the side chain in the C-direction to make it better resemble a peptidic substrate of the enzyme. However, the results for these compounds do support the earlier observation that a phenyl sulfonyl group is favored over an *N*-methyl sulfonyl group for inhibition (compare results for **14**/**15** and **20**/**21**).



Scheme 4. Reagents and conditions: (i) EtMgBr, THF, −10 °C to rt then $BrCH_2CO_2Et$, −10 °C to rt then aq NH_4Cl (61%); (ii) $POCl_3$, DMF, 1,2-DCE, reflux then $NaOAc{\cdot}3H_2O$, reflux (56%); (iii) NaOH, MeOH–H_2O (84%); (iv) L-LeuOMe.HCl, EDCI, HOBt, DIPEA (85%). (v) NaH, THF then $MeSO_2Cl$, −10 °C to rt (70%); (vi) $Zn(BH_4)_2$, Et2O, 0 °C (83%).

Table 1. Inhibition of α-chymotrypsin

Compound	% Inhibition at:	
	12.5 μg mL^{-1}	125 μg mL^{-1}
8a	10	0
8b	10	10
8c	0	0
8d	20	5
8e	15	5
8f	10	5
9a	5	0
9b	0	0
14	5	0
15	10	0
20	0	0
21	15	10
27	5	0

Conclusion

In summary, we have synthesised a range of *N*-acyl and *N*-sulfonylhydroxymetyhylpyrroles and shown them to provide a new class of inhibitor of α-chymotrypsin using a quick and convenient screening assay. The requirement, for inhibition activity, of a hydrophobic group in the *N*-substituent has also been demonstrated. We have yet to establish the mechanism by which this class of compound inhibit α-chymotrypsin, however, we postulate that it may occur via sequence b (Scheme 1) were Nu^- is an enzyme active site residue. What we do know is that compounds **4** (the postulated inactivating species) readily react with a nucleophile and are as such capable of inhibition. However, compounds **4** are too reactive to assay directly. Further work is in progress to characterise the exact mode of inhibition of these compounds and to better understand those structural factors that influence potency.

Experimental

Proton detected NMR spectra were obtained on either a Varian Unity 3000 spectrometer or a Varian XL300 spectrometer, both operating at 300 MHz. Carbon detected NMR were obtained on the XL300 spectrometer operating at 75 MHz. IR spectra were obtained using a Shimadzu 8201PC series FTIR. Mass spectrometry was performed on either a Kratos MS80 Mass Spectrometer or a Micromass LCT operating in Electrospray (ES) mode with 50:50 acetonitrile water as solvent. α-Chymotrypsin assays were carried out in microtitre plates (NUNC flat bottomed plates, GIBCO). Compounds **7b**,[12] **7c**,[1a] **8a**,[12] **8b**,[12] **8c**,[1a] and **22**[13] were prepared by literature methods.

α-Chymotrypsin assay

Solutions of the test compounds **8a**–**f**, **9a**–**b**, **14**, **15**, **20**, **21** and **27** were made to 125 and 12.5 μg mL^{-1} in methanol. Tris–HCl (50 μL of 0.4 M solution in water, pH 7.6), distilled water (50 μL), test solution (50 μL) and α-chymotrypsin (50 μL, Sigma ex-Bovine pancreas, 9 units mL^{-1} in 50 mM Tris–HCl buffer, pH 7.6) were added to each well of the microtitre plate. Incubation at 37 °C for 30 min was followed by the addition of *N*-succinyl-L-phenylalanine-4-nitroanilide (100 μL, 1 mg mL^{-1} solution in 50 mM Tris–HCl buffer, pH 7.6). The absorbance was read at 405 nm at $t=0$, and over approximately 3 h period of incubation at 37 °C when significant color change had taken place. Each sample was assayed in triplicate and average absorbances were used to calculate the percentage (%) inhibition. Sample blanks in which 50 mM Tris–HCl buffer, pH 7.6, replaced α-chymotrypsin were run concurrently.

General procedure A: *N*-Acylation of pyrroles using sodium hydride

To a stirred suspension of NaH (typically 1.26 mmol, 80% suspension in oil, washed twice with petroleum ether, 1.2 equiv) in THF (6 mL) under N_2 was added the pyrrole (typically 1.09 mmol) dissolved in THF (2 mL). After stirring at rt for 15 min, the electrophile (typically 1.2–1.4 equiv) in THF (2 mL) was slowly added and stirring was continued for 1 h at rt. Water (10 mL) was added, the THF was removed under reduced pressure and the aqueous residue was extracted with dichloromethane (DCM) (3×15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL), saturated aqueous brine (10 mL), dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica. See Experimental for details.

Modification to general procedure A

The electrophile (typically 1.2–1.4 equiv) in THF (2 mL) was slowly added to a cooled mixture (−10 to 0 °C) of the pyrrolyl anion, prepared as described above. Stirring was continued at −10 to 0 °C for 30 min and then for 1 h at rt, before the reaction mixture was worked up using the same method as described above.

General procedure B: Zinc borohydride reductions

To a solution of the pyrrole aldehyde (typically 0.16 mmol) in ether (10 mL) at 0 °C under N_2 was added $Zn(BH_4)_2$ (1 equiv of 0.14 M solution in ether). The resulting solution was stirred at 0 °C for 30 min, then water (2 mL) and 10% aqueous glacial acetic acid (2 mL) were carefully added to quench the reaction. The separated aqueous phase was extracted with DCM (2×10 mL) and the combined organic phases were washed with water (2×10 mL), saturated aqueous brine (10 mL), dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica. See Experimental for details.

General procedure C: Sodium borohydride reductions

To a solution of the pyrrole ketone (typically 0.20 mmol) in MeOH (10 mL) at 0 °C under N_2 was added $NaBH_4$ (15 equiv). The resulting solution was stirred at 0 °C for 30 min, then diluted with DCM (10 mL), washed with water (2×10 mL), and the organic layer dried and evaporated under reduced pressure. The residue was purified by flash chromatography on silica. See experimental for details.

General procedure D: Hydrolysis of pyrrole esters using sodium hydroxide

A solution of the pyrrole ester (typically 1.22 mmol) in 50% aq MeOH (4 mL) containing NaOH (2.5 equiv) was stirred at 40 °C for 1 h. Water (10 mL) was then added, and the MeOH was removed under reduced pressure. The aqueous solution was washed with ether (10 mL), cooled to 5 °C and acidified with 50% aqueous H_2SO_4. The resulting solution was extracted with ether (3×15 mL), and the combined ethereal extracts were washed with saturated aqueous brine (10 mL), dried and evaporated under reduced pressure. See Experimental for details.

General procedure E: Peptide couplings using EDCI

To a stirred solution (~0.1 M) of the pyrrole carboxylic acid (typically 1.14 mmol) and the L-amino acid ester hydrochloride (1.1 equiv) in DCM (~11 mL) under N_2 at rt were added EDCI (1.3 equiv) and HOBt (1.5 equiv). DIPEA (1.1 equiv) was added and the reaction mixture was stirred for 16 h. The solution was then diluted with DCM (10 mL), washed with 3 M aqueous HCl (2×10 mL), water (2×10 mL), dried and evaporated under reduced pressure. The resultant oil was purified by flash chromatography on silica. See Experimental for details.

1-(*N*-Phthalyl-L-leucinyl)pyrrole-2-carboxaldehyde (7a). To a stirred suspension of NaH (7 mg, 0.23 mmol in 80% suspension in oil, washed twice with petroleum ether, 1.1 equiv) in THF (5 mL) under N_2 was added 2-formylpyrrole **6** (20 mg, 0.21 mmol) dissolved in THF (1 mL). To the ice-cooled mixture was added a solution of *N*-phthalyl-L-leucine acid fluoride[14] (61 mg, 0.23 mmol, 1.1 equiv) in THF (4 mL) over 15 min. The mixture was left to stir at 0 °C for 30 min, and at rt overnight. The mixture was then diluted with EtOAc (10 mL), washed with 2 M aq $KHSO_4$ (10 mL), water (10 mL), dried and evaporated under reduced pressure. Flash chromatography on silica (EtOAc:petroleum ether, 1:4) gave **7a** (62 mg, 87%) as a pale-yellow oil. Spectral data as reported.[12]

1-(Phenylsulfonyl)pyrrole-2-carboxaldehyde (7d). General procedure A was carried out using 2-formylpyrrole **6** (50 mg, 0.53 mmol) and phenylsulfonyl chloride (81 μL, 0.63 mmol, 1.2 equiv). Flash chromatography on silica (EtOAc:petroleum ether, 1:3) gave **7d** (121 mg, 97%) as a white solid: mp 81 °C (lit.[15] 79.5–80.5 °C).

1-(2-Phenylethenyl)pyrrole-2-carboxaldehyde (7e). The modified general procedure A was carried out using 2-formylpyrrole **6** (50 mg, 0.53 mmol) and β-*trans*-styrenesulfonyl chloride (128 mg, 0.63 mmol, 1.2 equiv). Flash chromatography on silica (EtOAc:petroleum ether, 1:4) gave **7e** (77 mg, 56%) as a pale-yellow solid. An analytical sample was obtained by recrystallisation from EtOAc/petroleum ether to give a white crystalline solid: mp 88 °C. ^{1}H NMR ($CDCl_3$) δ 6.41 (m, 1H, pyrrole H4), 7.21 (m, 1H, pyrrole H3), 7.40–7.47 (m, 4H, C*H*Ph and arom), 7.54 (m, 2H, arom), 7.62 (m, 1H, pyrrole H5), 7.81 (d, J = 15.6 Hz, 1H, SO_2CH), 9.79 (s, 1H, C*H*O); ^{13}C NMR ($CDCl_3$) δ 111.6, 123.5, 127.5, 128.9, 129.1, 129.6, 131.4, 132.0, 133.1, 146.0, 178.2. IR ($CHCl_3$) 2837, 1682, 1612 cm^{-1}. Anal. calcd for $C_{13}H_{11}NO_3S$: C, 59.76; H, 4.24; N, 5.36. Found: C, 59.74; H, 4.16; N, 5.30.

1-(2-Phenylethanesulfonyl)pyrrole-2-carboxaldehyde (7f). The modified general procedure A was carried out using 2-formylpyrrole **6** (50 mg, 0.53 mmol) and 2-phenylethanesulfonyl chloride (129 mg, 0.63 mmol, 1.2 equiv). Flash chromatography on silica (EtOAc:petroleum ether,

1:4) gave **7f** (116 mg, 84%) as a pale-pink solid: mp 61–63 °C. ^{1}H NMR ($CDCl_3$) δ 3.08 (m, 2H, CH_2Ph), 4.10 (m, 2H, SO_2CH_2), 6.38 (m, 1H, pyrrole H4), 7.12–7.30 (m, 6H, pyrrole H3 and arom), 7.56 (m, 1H, pyrrole H5), 9.68 (s, 1H, C*H*O); ^{13}C NMR ($CDCl_3$) δ 29.3, 55.8, 111.5, 127.1, 128.2, 128.8, 129.0, 131.0, 133.1, 136.2, 178.2; IR ($CHCl_3$) 1680 cm^{-1}. HRMS calcd for $C_{13}H_{13}NO$ (M-SO_2) 199.0997, found 199.0994.

2-Hydroxymethyl-1-(phenylsulfonyl)pyrrole (8d). The *N*-phenylsulfonylpyrrole **7d** (50 mg, 0.21 mmol) was reduced with $Zn(BH_4)_2$ by general procedure B. Flash chromatography on silica (EtOAc:petroleum ether, 1:2) gave **8d** (46 mg, 92%) as a pale-pink solid: mp 41–42 °C. ^{1}H NMR ($CDCl_3$) δ 2.57 (bs, 1H, O*H*), 4.61 (s, 2H, CH_2OH), 6.24–6.28 (m, 2H, pyrrole H4 andpyrrole H3), 7.28 (m, 1H, pyrrole H5), 7.49–7.65 (m, 3H, arom), 7.82 (m, 2H, arom); ^{13}C NMR ($CDCl_3$) δ 56.8, 112.0, 115.3, 123.6, 126.6, 129.5, 134.0, 134.6, 139.0. IR ($CHCl_3$) 3578, 1369 cm^{-1}. HRMS calcd for $C_{11}H_{11}NO_3S$ 237.0460, found 237.0458.

2-Hydroxymethyl-1-(2-phenylethenylsulfonyl)pyrrole (8e). The *N*-styrenesulfonylpyrrole **7e** (50 mg, 0.19 mmol) was reduced with $Zn(BH_4)_2$ by general procedure B. Flash chromatography on silica (EtOAc:petroleum ether, 1:3) gave **8e** (48 mg, 95%) as a pink solid: mp 76–77 °C; ^{1}H NMR ($CDCl_3$) δ 2.64 (bs, 1H, O*H*), 4.73 (s, 2H, CH_2OH), 6.24 (m, 1H, pyrrole H4), 6.30 (m, 1H, pyrrole H3), 7.02 (d, J = 15.6 Hz, 1H, C*H*Ph), 7.18 (m, 1H, pyrrole H5), 7.36–7.48 (m, 5H, arom), 7.63 (d, J = 15.6 Hz, 1H, SO_2CH); ^{13}C NMR ($CDCl_3$) δ 56.7, 111.6, 115.2, 123.0, 124.3, 128.7, 129.1, 131.5, 131.7, 134.1, 143.4; IR ($CHCl_3$) 3585, 3026, 1614 cm^{-1}. HRMS calcd for $C_{13}H_{13}NO_3S$ 263.0616, found 263.0616.

2-Hydroxymethyl-1-(2-phenylethanesulfonyl)pyrrole (8f). The *N*-phenylethanesulfonylpyrrole **7f** (50 mg, 0.19 mmol) was reduced with $Zn(BH_4)_2$ by general procedure B. Flash chromatography on silica (EtOAc:petroleum ether, 1:3) gave **8f** (47 mg, 94%) as a colourless oil: ^{1}H NMR ($CDCl_3$) δ 2.47 (bs, 1H, O*H*), 2.99 (m, 2H, CH_2Ph), 3.70 (m, 2H, SO_2CH_2), 4.76 (s, 2H, CH_2OH), 6.23 (m, 1H, pyrrole H4), 6.32 (m, 1H, pyrrole H3), 7.11–7.31 (m, 6H, pyrrole H5 and arom); ^{13}C NMR ($CDCl_3$) δ 29.3, 56.7 (2×C), 111.1, 115.6, 124.0, 127.2, 128.3, 128.9, 133.8, 136.6. IR ($CHCl_3$) 3578, 1369 cm^{-1}. HRMS calcd for $C_{13}H_{15}NO_3S$ 265.0773, found 265.0771.

2 - Chloromethyl - 1 - (phenylsulfonyl)pyrrole (9a). Mesyl chloride (1.5 equiv) was added to an ice cooled solution of **8d** (30 mg, 0.13 mmol) in DCM (2 mL) containing DIPEA (1.5 equiv). Stirring was continued at 0 °C for 20 min and for a further 30 min at rt. The solution was diluted with DCM (10 mL), washed with ice-cold water (10 mL), cold 10% aq HCl (10 mL), and saturated aqueous $NaHCO_3$ (10 mL). The organic phase was then dried and evaporated under reduced pressure. The residual oil was eluted through a short plug of silica (EtOAc:petroleum ether, 1:1) to give **9a** (quantitative) as a white solid: mp 66 °C. ^{1}H NMR ($CDCl_3$) δ 4.84 (s, 2H, CH_2Cl), 6.26 (m, 1H, pyrrole H4), 6.38 (m, 1H, pyrrole H3), 7.34 (m, 1H, pyrrole H5), 7.48–7.64 (m, 3H, arom), 7.89 (m, 2H, arom); ^{13}C NMR ($CDCl_3$) δ 37.2, 111.8, 117.1, 124.5, 127.1, 129.3, 134.0, 138.8, 142.6. HRMS calcd for $C_{11}H_{10}NO_2S$ (M-Cl) 220.0432, found 220.0435.

***N*-Phthalyl-L-leucine pyrrol-2-ylmethyl ester (9b).** The hydroxymethylpyrrole **8d** (30 mg, 0.13 mmol), DMAP (15 mg, 0.13 mmol, 1 equiv) and DIPEA (26 μL, 0.15 mmol, 1.2 equiv) were dissolved in DCM (8 mL) at rt. *N*-Phthalyl-L-leucine acid fluoride[10] (40 mg, 0.15 mmol, 1.2 equiv) dissolved in DCM (2 mL) was added and the resultant solution was stirred for 24 h under N_2. EtOAc (10 mL) was added and the mixture was washed with 10% aqueous citric acid (10 mL), water (2×10 mL), dried and evaporated under reduced pressure. Flash chromatography on silica (EtOAc:petroleum ether, 1:2) gave **9b** (55 mg, 90%) as a colourless oil which solidified at 0 °C. An analytical sample was obtained by recrystallisation from EtOAc/petroleum ether to give a white solid: mp 112 °C. ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 6.3 Hz, 3H, CHMe_2), 0.89 (d, J = 6.3 Hz, 3H, CHMe_2), 1.43 (m, 1H, C*H*Me$_2$) 1.75 (m, 1H, CH_2CHMe$_2$), 2.29 (m, 1H, CH_2CHMe$_2$), 4.80 (m, 1H, α*H*), 5.30 (m, 2H, CH_2O), 6.25 (m, 1H, pyrrole H4), 6.37 (m, 1H, pyrrole H3), 7.32 (m, 1H, pyrrole H5), 7.52–7.87 (m, 9H, Pht Hs and arom); ^{13}C NMR ($CDCl_3$) δ 20.9, 23.1, 25.0, 37.0, 50.7, 58.8, 111.8, 117.9, 123.5, 124.3, 126.7, 128.3, 129.5, 131.8, 134.0, 134.1, 139.2, 167.7, 169.4. IR ($CHCl_3$) 1776, 1742, 1717 cm^{-1}. Anal. calcd for $C_{25}H_{24}N_2O_6S$: C, 62.49; H, 5.03; N, 5.83. Found: C, 62.50; H, 5.33; N, 5.96.

Methyl 4-oxo-4-(1*H*-pyrrol-2-yl)butanoate (11). A solution of pyrrole (1.50 g, 22.4 mmol) in ether (9 mL) was added dropwise to MeMgI (11.74 mL of 2.0 M solution in ether, 23.5 mmol, 1.05 equiv) under N_2 so as to cause slight reflux. The solution was then heated at reflux for an additional 30 min. After cooling to rt, methyl succinyl chloride (2.75 mL, 22.4 mmol, 1 equiv) in ether (6 mL) was added, and the resulting mixture was heated at reflux for 1 h. The reaction was left overnight, and then poured into cold water. The aqueous and ether layers were separated, and the aqueous phase was extracted with ether (3×10 mL). The combined ethereal layers were washed with water (2×10 mL), dried and evaporated under reduced pressure. The resulting residue was distilled at reduced pressure (oil pump) to give **11** (1.97 g, 49%) as a yellow solid. An analytical sample was obtained by recrystallisation from petroleum ether to give white crystals: mp 49 °C. ^{1}H NMR ($CDCl_3$) δ 2.74 (t, J = 6.8 Hz, 2H, CH_2CO_2Me), 3.16 (t, J = 6.8 Hz, 2H, COCH_2), 3.69 (s, 3H, CO_2Me), 6.27 (m, 1H, pyrrole H4), 6.99 (m, 1H, pyrrole H3), 7.05 (m, 1H, pyrrole H5), 10.20 (bs, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.2, 32.4, 51.7, 110.6, 116.6, 125.1, 131.3, 173.3, 188.5. IR ($CHCl_3$) 3452, 3285, 1736, 1647 cm^{-1}. Anal. calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.62; H, 6.07; N, 7.58.

Methyl 4-oxo-4-[1-(methanesulfonyl)pyrrol-2-yl]butanoate (12). General procedure A was carried out using the pyrrole **11** (60 mg, 0.33 mmol) and mesyl chloride (37 μL, 0.46 mmol, 1.4 equiv). Flash chromatography on silica (EtOAc:petroleum ether, 1:2), followed by recrystallisation from petroleum ether, gave **12** (74 mg, 86%) as fine

white needles: mp 92 °C. ^{1}H NMR ($CDCl_3$) δ 2.75 (t, J = 6.6 Hz, 2H, CH_2CO$_2$Me), 3.18 (t, J = 6.6 Hz, 2H, COCH_2), 3.70 (s, 3H, CO$_2$*Me*), 3.72 (s, 3H, SO$_2$*Me*), 6.31 (m, 1H, pyrrole H4), 7.21 (m, 1H, pyrrole H3), 7.57 (m, 1H, pyrrole H5); ^{13}C NMR ($CDCl_3$) δ 27.6, 33.6, 42.8, 51.6, 110.0, 124.1, 129.6, 132.3, 172.9, 187.6. IR ($CHCl_3$) 1734, 1676 cm^{-1}. HRMS calcd for $C_{10}H_{13}NO_5S$ 259.0515, found 259.0511.

Methyl 4-oxo-4-[1-(phenylsulfonyl)pyrrol-2-yl]butanoate (13). General procedure A was carried out using the pyrrole **11** (60 mg, 0.33 mmol) and phenylsulfonyl chloride (51 μL, 0.40 mmol, 1.2 equiv). Flash chromatography on silica (EtOAc:petroleum ether, 1:2), followed by recrystallisation from EtOAc/petroleum ether, gave **13** (46 mg, 43%) as fine white crystals: mp 139–140 °C; ^{1}H NMR ($CDCl_3$) δ 2.61 (t, J = 6.8 Hz, 2H, CH_2CO$_2$Me), 3.03 (t, J = 6.8 Hz, 2H, COCH_2), 3.61 (s, 3H, CO$_2$*Me*), 6.35 (m, 1H, pyrrole H4), 7.12 (m, 1H, pyrrole H3), 7.48–7.62 (m, 3H, arom), 7.80 (m, 1H, pyrrole H5), 7.97 (m, 2H, arom); ^{13}C NMR ($CDCl_3$) δ 27.9, 33.8, 51.7, 110.5, 123.6, 128.1, 128.7, 130.2, 132.8, 133.6, 138.8, 142.7; IR ($CHCl_3$) 1734, 1682 cm^{-1}; HRMS calcd for $C_{15}H_{15}NO_5S$ 321.0671, found 321.0679.

Methyl 4-hydroxy-4-[1-(methanesulfonyl)pyrrol-2-yl]butanoate (14). The *N*-mesylpyrrole **12** (51 mg, 0.20 mmol) was reduced with $NaBH_4$ by general procedure C. Flash chromatography on silica (EtOAc:petroleum ether, 1:1) gave **14** (44 mg, 85%) as a colourless oil which solidified at 0 °C. An analytical sample was obtained by recrystallisation from petroleum ether to give white needles: mp 70 °C. ^{1}H NMR ($CDCl_3$) δ 2.24 (m, 2H, CHOHCH_2), 2.57 (m, 2H, CH_2CO$_2$Me), 2.98 (bs, 1H, O*H*), 3.29 (s, 3H, SO$_2$*Me*), 3.70 (s, 3H, CO$_2$*Me*), 5.06 (t, J = 6.6 Hz, 1H, C*H*OH), 6.25 (m, 1H, pyrrole H4), 6.34 (m, 1H, pyrrole H3), 7.15 (m, 1H, pyrrole H5); ^{13}C NMR ($CDCl_3$) δ 30.2, 30.7, 43.0, 51.8, 64.8, 111.2, 112.2, 123.1, 136.7, 174.2. IR ($CHCl_3$) 3580, 1732 cm^{-1}. HRMS calcd for $C_{10}H_{15}NO_5S$ 261.0671, found 261.0671.

Methyl 4-hydroxy-4-[1-(phenylsulfonyl)pyrrol-2-yl]butanoate (15). The *N*-phenylsulfonylpyrrole **13** (25 mg, 0.08 mmol) was reduced with $NaBH_4$ by general procedure C. Flash chromatography on silica (EtOAc:petroleum ether, 2:3) gave **15** (23 mg, 90%) as a pale-purple oil. ^{1}H NMR ($CDCl_3$) δ 2.06 (m, 2H, CHOHCH_2), 2.40 (m, 2H, CH_2CO$_2$Me), 3.59 (s, 3H, CO$_2$*Me*), 4.84 (m, 1H, C*H*OH), 6.19 (m, 1H, pyrrole H4), 6.25 (m, 1H, pyrrole H3), 7.22 (m, 1H, pyrrole H5), 7.42–7.57 (m, 3H, arom), 7.71 (m, 2H, arom); ^{13}C NMR ($CDCl_3$) δ 30.2, 30.6, 51.6, 64.7, 111.9, 112.6, 123.6, 126.5, 129.5, 134.0, 137.6, 139.1, 173.9. IR ($CHCl_3$) 3578, 1776, 1732 cm^{-1}. HRMS calcd for $C_{15}H_{15}NO_4S$ (M−H_2O) 305.0722, found 305.0723.

***N*-[4-Oxo-4-(*1H*-pyrrol-2-yl)]butanoyl-L-leucine methyl ester (17).** The pyrrole ester **11** (300 mg, 1.66 mmol) was hydrolysed with NaOH by general procedure D to give **16** (217 mg, 78%) as a yellow solid, which was not purified further: mp 141 °C (lit.[16] 140–141 °C). A sample of this material (190 mg, 1.14 mmol) was coupled with L-leucine methyl ester hydrochloride (227 mg, 1.25 mmol, 1.1 equiv) according to general procedure E. Flash chromatography on silica (EtOAc:petroleum ether, 1:1) gave **17** (312 mg, 93%) as a mauve solid. An analytical sample was obtained by recrystallisation from EtOAc/petroleum ether to give colorless crystals: mp 100–101 °C. ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 5.9 Hz, 6H, CHMe$_2$), 1.51–1.67 (m, 3H, CH$_2$CHMe$_2$), 2.68 (m, 2H, CH$_2$CONH), 3.18 (m, 2H, COCH$_2$), 3.72 (s, 3H, CO$_2$Me), 4.66 (m, 1H, αH), 6.27 (m, 1H, pyrrole H4), 6.77 (d, J = 7.8 Hz, 1H, CONH), 6.98 (m, 1H, pyrrole H3), 7.04 (m, 1H, pyrrole H5), 10.02 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.7, 24.8, 30.3, 33.0, 41.7, 50.6, 52.2, 110.6, 116.8, 124.9, 131.4, 172.0, 173.9, 189.2. IR ($CHCl_3$) 3450, 3344, 1740, 1672, 1645 cm^{-1}. Anal. calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.09; H, 7.60; N, 9.46.

***N*-{4-Oxo-4-[1-(methanesulfonyl)pyrrol-2-yl]}butanoyl-L-leucine methyl ester (18).** General procedure A was carried out using **17** (60 mg, 0.20 mmol) and mesyl chloride (23 μL, 0.29 mmol, 1.4 equiv). Flash chromatography on silica (EtOAc:petroleum ether, 2:1) gave **18** (38 mg, 50%) as a white solid: mp 106–107 °C. ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 5.9 Hz, 3H, CHMe_2), 0.93 (d, J = 6.3 Hz, 3H, CHMe_2), 1.51–1.71 (m, 3H, CH_2C*H*Me$_2$), 2.65 (m, 2H, CH_2CONH), 3.22 (m, 2H, COCH_2), 3.71 (s, 3H, CO$_2$*Me*), 3.72 (s, 3H, SO$_2$*Me*), 4.61 (m, 1H, α*H*), 6.11 (d, J = 8.3 Hz, 1H, CON*H*), 6.30 (m, 1H, pyrrole H4), 7.22 (m, 1H, pyrrole H3), 7.57 (m, 1H, pyrrole H5); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.7, 24.8, 29.9, 34.3, 41.6, 43.1, 50.8, 52.2, 110.3, 124.5, 129.9, 132.5, 171.5, 173.4, 188.4; IR ($CHCl_3$) 3435, 1740, 1672 cm^{-1}. HRMS calcd for $C_{16}H_{24}N_2O_6S$ 372.1355, found 372.1347.

***N*-{4-Hydroxy-4-[1-(methanesulfonyl)pyrrol-2-yl]}butanoyl-L-leucine methyl esters (20).** The *N*-mesylpyrrole **18** (54 mg, 0.14 mmol) was reduced with $NaBH_4$ by general procedure C. Flash chromatography on silica (EtOAc:petroleum ether, 5:2) gave **20** (48 mg, 89%) as a mixture of epimers (2:1 by ^{1}H NMR), as an oil. ^{1}H NMR ($CDCl_3$) of major isomer, δ 0.94 (d, J = 6.3 Hz, 6H, CHMe_2), 1.51–1.68 (m, 3H, CH_2C*H*Me$_2$), 2.24 (m, 2H, CHOHCH_2), 2.51 (m, 2H, CH_2CONH), 3.32 (s, 3H, SO$_2$*Me*), 3.74 (s, 3H, CO$_2$*Me*), 4.62 (m, 1H, α*H*), 5.07 (m, 1H, C*H*OH), 6.21–6.25 (m, 2H, CON*H* and pyrrole H4), 6.34 (m, 1H, pyrrole H3), 7.14 (m, 1H, pyrrole H5); selected ^{1}H NMR of minor isomer, δ 3.31 (s, 3H, SO$_2$*Me*); ^{13}C NMR ($CDCl_3$) of major isomer, δ 21.9, 22.7, 24.8, 30.6, 32.9, 41.4, 43.0, 50.8, 52.3, 64.8, 111.1, 112.1, 122.9, 137.0, 173.1, 173.6; selected ^{13}C NMR of minor isomer, δ 30.7, 33.0, 41.5, 50.8, 65.1, 173.1, 173.5. IR ($CHCl_3$) 3570, 3433, 3306, 1740, 1666 cm^{-1}; HRMS calcd for $C_{16}H_{24}N_2O_5S$ (M−H_2O) 356.1406, found 356.1407.

***N*-{4-Hydroxy-4-[1-(phenylsulfonyl)pyrrol-2-yl]}butanoyl-L-leucine methyl ester (21).** General procedure A was carried out using the pyrrole **17** (50 mg, 0.17 mmol) and phenylsulfonyl chloride (52 μL, 0.41 mmol, 2.4 equiv). Flash chromatography on silica (EtOAc:petroleum ether, 1:1) gave an inseparable mixture of **17** and **19** (1:5 by ^{1}H NMR) which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) of **19** assigned from the mixture, δ 0.88 (m, 6H, CHMe_2), 1.42–1.62 (m, 3H, CH_2C*H*Me$_2$), 2.51 (m, 2H, CH_2CONH), 3.07 (m, 2H,

$COCH_2$), 3.68 (s, 3H, CO_2Me), 4.52 (m, 1H, αH), 6.03 (d, $J=8.3$ Hz, 1H, CONH), 6.34 (m, 1H, pyrrole H4), 7.13 (m, 1H, pyrrole H3), 7.47–7.61 (m, 3H, arom), 7.79 (m, 1H, pyrrole H5), 7.96 (m, 2H, arom). The preceeding sample of *N*-phenylsulfonylpyrrole **19** (48 mg, 0.11 mmol) was reduced with $NaBH_4$ by general procedure C. Flash chromatography on silica (EtOAc:petroleum ether, 2:1) gave **21** (28 mg, 38% overall for both steps) as a mixture of epimers (2:1 by ^1H NMR). An analytical sample was obtained by recrystallisation from EtOAc/petroleum ether to give colorless crystals: mp 99–101 °C. ^1H NMR ($CDCl_3$) of major isomer, δ 0.94 (d, $J=5.9$ Hz, 6H, $CHMe_2$), 1.51–1.67 (m, 3H, CH_2CHMe_2), 2.15 (m, 2H, $CHOHCH_2$), 2.42 (m, 2H, CH_2CONH), 3.75 (s, 3H, CO_2Me), 4.63 (m, 1H, αH), 4.96 (m, 1H, CHOH), 6.10 (d, $J=7.3$ Hz, 1H, CONH), 6.25 (m, 1H, pyrrole H4), 6.33 (m, 1H, pyrrole H3), 7.26 (m, 1H, pyrrole H5), 7.48–7.63 (m, 3H, arom), 7.78 (m, 2H, arom); selected ^1H NMR of minor isomer, δ 3.73 (s, 3H, CO_2Me); ^{13}C NMR ($CDCl_3$) of major isomer, δ 21.9, 22.7, 24.8, 31.0, 32.9, 41.6, 50.8, 52.3, 65.3, 112.0, 112.7, 123.4, 126.5, 129.5, 134.0, 138.0, 139.1, 172.9, 173.5; selected ^{13}C NMR of minor isomer, δ 31.0, 65.4, 126.5. IR ($CHCl_3$) 3568, 3433, 3317, 1740, 1670 cm^{-1}. Anal. calcd for $C_{21}H_{28}N_2O_6S$: C, 57.78; H, 6.47; N, 6.42. Found: C, 57.86; H, 6.25; N, 6.51.

Ethyl 2-(5-formyl-1*H*-pyrrol-2-yl)ethanoate (23). $POCl_3$ (1.1 equiv) was added dropwise over 15 min to a solution of DMF (1.1 equiv) cooled to 10–20 °C under N_2. 1,2-Dichloroethane (8 mL) was added, followed by a solution of the pyrrole **22**[9] (2.19 g, 14.3 mmol) in 1,2-dichloroethane (8 mL) over 1 h. The mixture was heated at reflux for 15 min, cooled to 20 °C, treated with a solution of $NaOAc.3H_2O$ (5 equiv) in water (30 mL) and heated at reflux for a further 15 min. The 1,2-dichloroethane layer was separated, and the aqueous phase was extracted with ether (3×15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (3×15 mL), dried and evaporated under reduced pressure. The residue was distilled under high vacuum to give **23** (1.45 g, 56%) as a pale-orange solid. An analytical sample was obtained by sublimation under reduced pressure to give a white crystalline solid: mp 73–75 °C. ^1H NMR ($CDCl_3$) δ 1.29 (t, $J=7.3$ Hz, 3H, $CO_2CH_2CH_3$), 3.72 (s, 2H, CH_2CO_2), 4.22 (q, $J=7.3$ Hz, 2H, $CO_2CH_2CH_3$), 6.18 (m, 1H, pyrrole H3), 6.90 (m, 1H, pyrrole H4), 9.45 (s, 1H, CHO), 9.88 (bs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 33.4, 61.4, 111.0, 122.2, 132.6, 133.8, 169.6, 178.7. IR ($CHCl_3$) 3433, 1732, 1651 cm^{-1}. Anal. calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.89; H, 5.99, N, 7.71.

***N*-[2-(5-Formyl-1*H*-pyrrol-2-yl)]ethanoyl-L-leucine methyl ester (25).** The pyrrole ester **23** (300 mg, 1.66 mmol) was hydrolysed with NaOH by general procedure D to give **24** (213 mg, 84%) as a yellow solid that was not purified further: mp 123–124 °C. ^1H NMR (acetone-d_6) δ 3.86 (s, 2H, CH_2CO_2), 6.33 (dd, $J=3.4$, 2.4 Hz, 1H, pyrrole H3), 7.08 (dd, $J=3.4$, 2.4 Hz, 1H, pyrrole H4), 9.43 (s, 1H, CHO), 11.49 (bs, 1H, NH). Thus obtained **24** (210 mg, 1.37 mmol) was coupled with L-leucine methyl ester hydrochloride (274 mg, 1.51 mmol, 1.1 equiv) according to general procedure E. Flash chromatography on silica (EtOAc:petroleum ether, 2:1) gave **25** (326 mg, 85%) as a pale-orange solid: mp 54 °C. ^1H NMR ($CDCl_3$) δ 0.88 (d, $J=5.9$ Hz, 6H, $CHMe_2$), 1.48–1.64 (m, 3H, CH_2CHMe_2), 3.69 (s, 2H, CH_2CO_2), 3.72 (s, 3H, CO_2Me), 4.63 (m, 1H, αH), 6.24 (dd, $J=3.9$, 2.4 Hz, 1H, pyrrole H3), 6.79 (d, $J=7.8$ Hz, 1H, CONH), 6.95 (dd, $J=3.9$, 2.4 Hz, 1H, pyrrole H4), 9.38 (s, 1H, CHO), 10.89 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 21.6, 22.5, 24.7, 35.4, 40.9, 50.9, 52.2, 111.2, 122.9, 132.4, 135.5, 168.8, 173.6, 178.7. IR ($CHCl_3$) 3422, 3298, 1744 cm^{-1}. Anal. calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.16; H, 7.20; N, 9.84.

***N*-{2-[5-Formyl-1-(methanesulfonyl)pyrrol-2-yl]}ethanoyl-L-leucine methyl ester (26).** The modified general procedure A was carried out using pyrrole **25** (50 mg, 0.18 mmol) and mesyl chloride (17 μL, 0.21 mmol, 1.2 equiv). Flash chromatography on silica (EtOAc:petroleum ether, 1:1) gave **26** (45 mg, 70%) as a pale-yellow oil. ^1H NMR ($CDCl_3$) δ 0.95 (d, $J=6.3$ Hz, 6H, $CHMe_2$), 1.53–1.80 (m, 3H, CH_2CHMe_2), 3.65 (s, 3H, SO_2Me), 3.74 (s, 3H, CO_2Me), 3.93 and 4.00 (ABq, $J=16.6$ Hz, 2H, CH_2CO), 4.64 (m, 1H, αH), 6.19 (d, $J=8.3$ Hz, 1H, CONH), 6.25 (d, $J=3.9$ Hz, 1H, pyrrole H3), 7.12 (d, $J=3.9$ Hz, 1H, pyrrole H4), 9.70 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 21.8, 22.8, 24.6, 36.2, 41.6, 42.4, 50.9, 52.4, 115.1, 126.7, 135.4, 138.6, 168.6, 173.3, 178.2. IR ($CHCl_3$) 3429, 3327, 1740 cm^{-1}. HRMS calcd for $C_{15}H_{22}N_2O_6S$ 358.1199, found 358.1190.

***N*-{2-[5-Hydroxymethyl-1-(methanesulfonyl)pyrrol-2-yl]}ethanoyl-L-leucine methyl ester (27).** The *N*-mesylpyrrole **26** (35 mg, 0.10 mmol) was reduced with $Zn(BH_4)_2$ by general procedure B. Flash chromatography on silica (EtOAc:petroleum ether, 2:1) gave **27** (29 mg, 83%) as an orange solid. An analytical sample was obtained by recrystallisation from methanol to give thin colourless needles: mp 150–151 °C. ^1H NMR (CD_3OD) δ 0.94 (m, 6H, $CHMe_2$), 1.55–1.81 (m, 3H, CH_2CHMe_2), 3.40 (s, 3H, SO_2Me), 3.70 (s, 3H, CO_2Me), 3.80 and 3.89 (ABq, $J=17.1$ Hz, 2H, CH_2CO), 4.47 (m, 1H, αH), 4.67 and 4.74 (ABq, $J=13.2$ Hz, 2H, CH_2OH), 6.09 (d, $J=3.4$ Hz, 1H, pyrrole H3), 6.22 (d, $J=3.4$ Hz, 1H, pyrrole H4), 8.30 (d, $J=7.8$ Hz, 1H, CONH); ^{13}C NMR (CD_3OD) δ 22.1, 23.6, 26.1, 36.7, 41.8, 42.8, 52.6, 53.0, 58.4, 114.7, 115.1, 132.3, 137.5, 173.2, 175.1. IR ($CHCl_3$) 1740, 1676 cm^{-1}. Anal. calcd for $C_{15}H_{24}N_2O_6S$: C, 49.99; H, 6.71; N, 7.77. Found: C, 49.70; H, 6.93; N, 7.50.

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7. The P_1 amino acid defines the point of cleavage of the substrate peptide where, by definition, hydrolysis occurs on the carboxyl side of this residue (for a definition of this nomenclature see: Schechter, I.; Berger, A. *Biochem. Biophys. Res. Commun.* 1967, *27*, 157).
8. The choice of protecting group (*N*-phthaloyl) and the amino acid (leucine) were dictated by ease of synthesis (unpublished results).
9. We have previously shown that an *N*-sulfonyl group is superior to an *N*-acyl group at deactivating a hydroxymethylpyrrole (see ref 1a). As a consequence these compounds tend to be more stable and are in many cases crystalline solids.
10. The use of the acid fluoride, rather than the acid chloride, gave a much better yield of the desired product. Acid fluorides have also been reported to minimise epimerisation at the amino acid stereogenic centre in reactions of this type (see ref 14).
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