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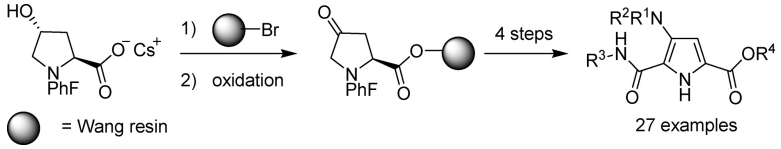

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Solid-Phase Synthesis of 3-Aminopyrrole-2,5-dicarboxylate Analogues

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An efficient strategy has been developed for the solid-phase parallel synthesis of 3-aminopyrrole-2,5-dicarboxylate analogues. A library of twenty-nine 2,3,5-trisubstituted pyrroles has been synthesized on Wang resin by a 5−6 step process. The attachment of (2*S*,4*R*)-4-hydroxy-*N*-(PhF)proline cesium salt (PhF = 9-(9-phenylfluorenyl)) to Wang bromide resin, followed by alcohol oxidation, produced the resin-bound 4-oxo-*N*-(PhF)prolinate as the pyrrole precursor. Resin-bound 3-aminopyrroles were synthesized by treatment of the oxo-*N*-(PhF)prolinate resin with different secondary amines and diversified at the 2-position by acylation with trichloroacetyl chloride and haloform reactions with primary amines. 3-Aminopyrrole-2,5-dicarboxylates were isolated in 81−99% purity and 51−99% yields after cleavage from the resin using TFA or sodium methoxide.

Introduction

Substituted pyrroles are commonly found in natural products,[1,2] drugs,[3,4] conducting materials,[5,6] and insecticides.[7] Amides derived from pyrrole-2-carboxylates are particularly important structural motifs in biologically active molecules likely because of their potential to engage in hydrogen-bond interactions with natural macromolecules. For example, polyamides formed from linking 4-aminopyrrole-2-carboxylates serve in the recognition of DNA by natural products, such as distamycin and netropsin (Figure 1) as well as by synthetic analogues that have exhibited antibiotic, antiviral, antimicrobial, and oncolytic properties.[8−16] Amide analogues of pyrrole carboxylates, such as **1** and **2**, have similarly served in the recognition of amino acids and peptides in water.[17,18] Moreover, 3-aminopyrrole-2-carboxylates, such as **3**, have exhibited anticonvulsant activity by blocking sodium channels in a frequency-dependent manner.[19] Recognizing the importance of 3- and 4-aminopyrrole-2-carboxylates, as well as pyrrole-2,5-dicarboxylates, as motifs for molecular recognition, we have developed a solid-phase strategy for the synthesis of 3-aminopyrrole-2,5-dicarboxylate analogues to provide a novel group of potential ligands and pharmacophores for the development of drugs and tools for chemical-biology.

The pyrrole ring system has been previously synthesized on solid supports by several methods. For example, lamellarins U and L (Figure 1) have been made by N-alkylation of a supported iodoacetate with 3,4-dihydro-6,7-dimethoxyisoquinoline followed by [3 + 2] cycloaddition.[20] Few solid-phase methods have, to the best of our knowledge, provided libraries of pyrrole analogues. For example, the cycloaddition of alkynes to solid-supported 1,3-dipoles (method A, Figure 2)[21−23] has been used to provide pyrrole libraries; however, regioisomeric mixtures were obtained using unsymmetrical

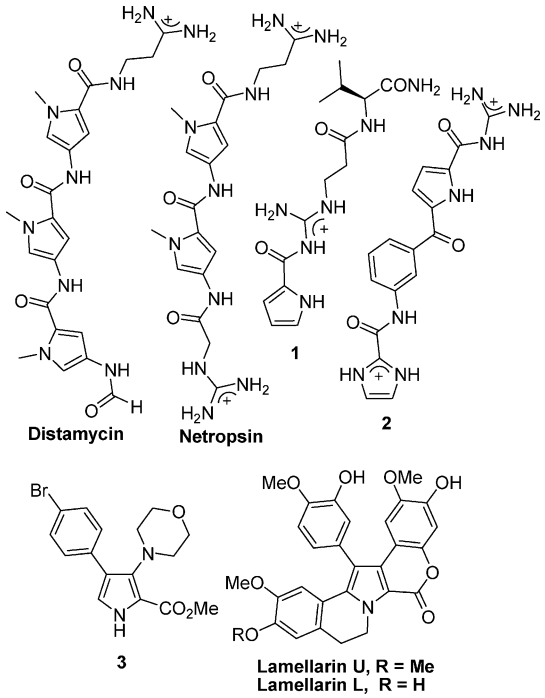

Figure 1. Representative examples of bioactive pyrrole 2-carboxylate analogues.

alkynes.[21] Hantzsch[24] cyclocondensations of resin-bound enaminones with α-bromoketones (method B, Figure 2)[25] has given access to a library of pyrroles; furthermore, related resin-supported Hantzsch methodology has successfully used cyclocondensations of nitroalkenes,[26] aldehydes and nitroalkanes,[26] and β-ketoamides.[27] The Paal−Knorr[28,29] condensation of polymer-supported 1,4-diketones with primary amines (method C, Figure 2) has produced tetrasubstituted pyrroles.[30] 1,3-Dipolar cycloadditions onto supported vinyl sulfones and the subsequent pyrrole annulation (method D, Figure 2) have delivered isoxazolinopyrrole-2-carboxylates.[31,32] Furthermore, pyrrole formation by the homocoupling of two solid-supported ketones has furnished a

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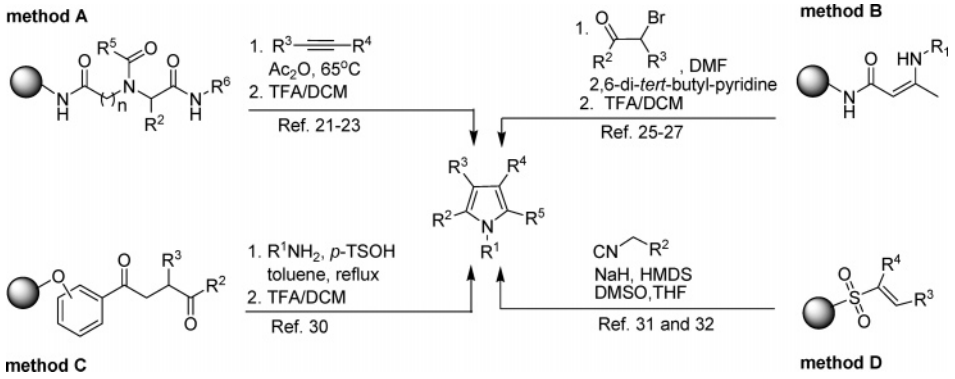


Figure 2. Methods for pyrrole library synthesis on solid support.

library of norbinaltorphimine derivatives as potential κ opioid receptor antagonists.[33,34] Finally, polymer-supported 2,5-dimethylpyrrole has been used as a protecting group to mask primary amines on resin.[35]

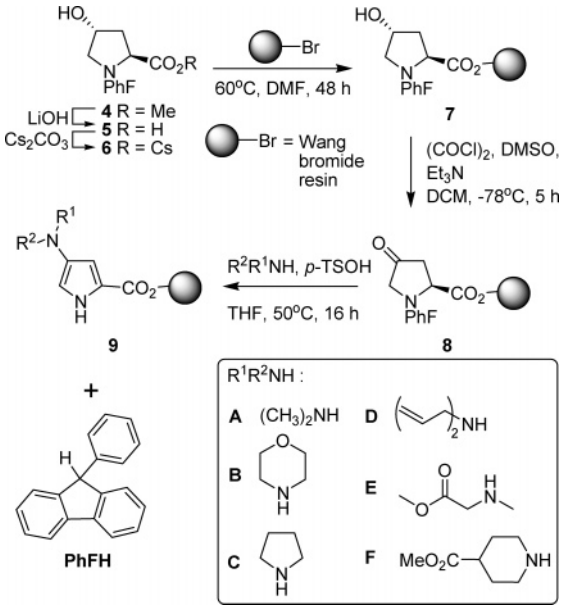
Previously, our group reported a solution-phase methodology for the synthesis of 4-amino-1*H*-pyrrole-2-carboxylates based on treatment of (2*S*)-*N*-PhF-4-oxoproline benzyl ester with different primary and secondary amines (PhF = 9-(9-phenylfluorenyl).[36] This methodology was later expanded to prepare pyrrolo[3,2-*d*]pyrimidines possessing various substituents at the pyrimidine nitrogens by solution-phase chemistry,[37] as well as by a solid-phase methodology featuring a cysteamine linkage to a pyrimidine nitrogen.[38,39] Employing the carboxylate of (2*S*)-*N*-PhF-4-oxoproline as the site of attachment to the solid support, we have now developed a strategy for synthesizing 3-aminopyrrole-2,5-dicarboxylate analogues. Diversification of the pyrrole ring was achieved by amination of the resin-bound ketone, electrophilic addition to the 2-position, and nucleophilic displacement or acidic conditions to cleave the carboxylate from the resin. A library of twenty-nine 3-aminopyrrole-2,5-dicarboxylates was synthesized by this process from manipulations of (2*S*,4*R*)-4-hydroxy-*N*-(PhF)proline on Wang resin.

Results and Discussion

(2*S*,4*R*)-4-Hydroxy-*N*-(PhF)proline **5** was synthesized in solution by hydrolysis of (2*S*,4*R*)-4-hydroxy-*N*-(PhF)proline methyl ester **4** using LiOH in a THF/methanol/water (3:2:1) solution (Scheme 1).[40] The corresponding cesium salt, **6**, was then prepared by treatment of acid **5** with 20% Cs_2CO_3 until pH 7 followed by lyophilization to provide a gray powder that was loaded onto the solid support.

4-(Bromomethyl)phenoxymethyl polystyrene (Wang bromide resin) was purchased from commercial sources or prepared from Wang resin by bromination with *N*-bromosuccinimide (NBS) and dimethyl sulfide in CH_2Cl_2 at 0 °C for 5 h.[41] The yellow Wang bromide resin obtained in this manner was characterized by IR spectroscopy. Formation of the bromide was inferred by the disappearance of the O−H stretching band at 3435 cm^{-1} and the appearance of a C−Br stretching band at 592 cm^{-1}. The loading of the bromo resin was evaluated by displacement with 2-naphthoic acid in the presence of DIPEA in CH_2Cl_2 at room temperature for 20 h, and then the resin-bound ester was treated twice with 50% TFA in CH_2Cl_2 at room temperature for 30 min.[41] Filtration

Scheme 1. Synthesis of 4-Aminopyrrole Carboxylate Resin **9**



of the resin and evaporation of the filtrate yielded pure 2-naphthoic acid, and the recovery from a measured amount of the brominated resin was used to ascertain the loading.

Resin-bound 4-hydroxy-*N*-(PhF)proline **7** was synthesized by the attachment of cesium salt **6** to Wang bromide resin in DMF at 60 °C for 48 h (Scheme 1). The loading was assessed at a later stage because TFA cleavage of the resin-bound proline also caused solvolysis of the acid-labile PhF protecting group. Qualitatively, ester formation was indicated using IR spectroscopy of resin samples pressed in KBr tablets. Sharp indicative signals were observed for the O−H and C═O stretching bands at 3438 and 1731 cm^{-1}, respectively; moreover, the C−Br band at 592 cm^{-1} disappeared. Unreacted acid **5** was recovered and recycled after filtration of the resin by evaporation of the filtrate and partitioning of the residue between EtOAc and 1 M NaH_2PO_4.

Resin-bound 4-oxo-*N*-(PhF)proline **8** was prepared by oxidation of hydroxyproline resin **7** with oxalyl chloride and DMSO at −78 °C for 4 h followed by treatment with Et_3N and additional agitation at −78 °C for 1 h. The resulting ketone, **8**, was identified by the presence of a second carbonyl band at 1751 cm^{-1} and the disappearance of the hydroxyl absorption at 3438 cm^{-1} in the IR spectrum.

Resin-bound 4-aminopyrroles, **9**, were produced by treatment of ketone **8** with a variety of secondary amines (800

Table 1. Yields of Isolated PhFH from Treatment of 4-Oxoproline Resin **8** with Secondary Amines

entry	R^2R^1NH	yield[a] (%)	yield[b] (%)	total yield[a,b] (%)
A	dimethylamine	71	4	75
B	morpholine	69	4	73
C	pyrrolidine	72	0	72
D	diallylamine	25	20	45
E	sarcosine methyl ester	55	13	68
F	isonipecotic acid methyl ester	33	15	48

[a] Isolated yield after first submission. [b] Isolated yield after second submission.

mol %) and a catalytic amount of *p*-TsOH (10 mol %) in dry THF at 50 °C for 18 h. The hydrochloride salts of secondary amines (800 mol %) were employed with Et_3N (780 mol %) without *p*-TsOH. Formation of the resin-bound pyrrole **9** was evaluated by the recovery of 9-phenyl-9*H*-fluorene (PhFH) after filtration of the resin, evaporation of the filtrate, and isolation by column chromatography with hexanes: EtOAc (90:10, $R_f = 0.7$). The relative reactivity of each amine (Table 1) was determined by treating 300 mg portions of the same batch of 4-oxoproline resin **8** with 800 mol % of the respective secondary amines and measurement of the PhFH isolated after column chromatography of the evaporated filtrate. Dimethylamine, morpholine, pyrrolidine, and diallylamine were chosen to attack the resin-bound 4-oxoproline **8** because they had all proven successful in the formation of amino pyrroles in solution. Sarcosine and isonipecotic methyl esters were also employed for potential diversification by subsequent modification of their ω-carboxylate group. Formation of amino pyrrole resin **9** was assessed by the recovery of PhFH after the submission of the oxoproline resin to the secondary amine. A single treatment of oxoproline resin **8** with dimethylamine, morpholine, and pyrrolidine (entries A−C, Table 1) gave high conversion; however, a second submission was necessary to obtain high conversion using diallylamine, sarcosine, and isonipecotic acid methyl esters (entries D−F, Table 1). Only traces of PhFH were retrieved upon treatment of resin **8** with MeNHOMe. The loading of resin-bound amino pyrrole **9** was ascertained on the basis of the amount of PhFH recovered, and it was used to determine the yield of final cleaved product.

2-Trichloroacteyl-3-amino-1*H*-pyrrole-5-carboxylate resin **10** was obtained by acylation of 4-aminopyrrole resin **9** with trichloroacetyl chloride in the presence of Et_3N in CH_2Cl_2 at room temperature for 4 h (Scheme 2). Trichloromethyl ketone resin **10** was used immediately in the next step after washing. Acylation of resin **9** using trichloroacetyl chloride without Et_3N was found to give product of lower purity after resin cleavage.

Resin-bound 2-carbamoyl-3-amino-1*H*-pyrrole-5-carboxylates, **12**, were synthesized by the exposure of trichloromethyl ketone resin **10** under haloform releasing conditions to solutions of primary amine in THF at room temperature for 1 h. The conversion of aminopyrrole resin **12** to 2-carbamoyl-3-amino-1*H*-pyrrole-5-carboxylic acid **13** was ascertained by LCMS analysis of the product after cleavage of a small portion of the resin (Scheme 2). Amines bearing aromatic (benzylamine), ether (methoxyethylamine), olefin (allyl-

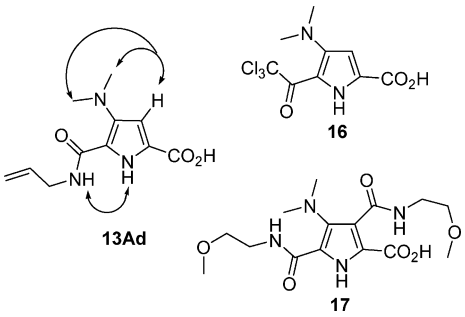
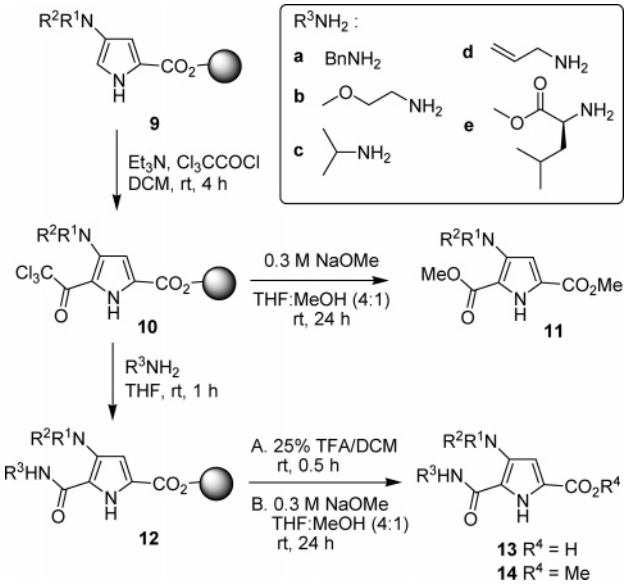


Figure 3. Observed NOE upon saturation of pyrrole protons of 2-allylcarbamoyl-3-(dimethylamino)-1*H*-pyrrole-5-carboxylic acid (**13Ad**), as well as the structures of 2-trichloromethyl ketone-3-(dimethylamino)-1*H*-pyrrole-5-carboxylic acid (**16**) and 2,4-di-(methoxyethylcarbamoyl)-3-(dimethylamino)-1*H*-pyrrole-5-carboxylic acid (**17**).

Scheme 2. Solid-Phase Synthesis of 3-Aminopyrrole-2,5-dicarboxylates



amine), alkyl branched (isopropylamine), and ester (L-Leu-OMe) groups were examined to provide a diverse series of amides. Attempts to effect the corresponding haloform reaction with secondary amines (morpholine, diethylamine, and di(hydroxyethyl) amine) using dimethylamino pyrrole resin did not give the expected tertiary amido pyrroles as indicated by the lack of the corresponding molecular ion in the LCMS analysis; instead, the ion for 2-trichloroacetyl-3-(dimethylamino)-1*H*-pyrrole-5-carboxylic acid **16** was detected after cleavage of the resin. The exposure of recovered trichloromethyl ketone resin **10** to benzylamine, after failed treatment with morpholine, under similar conditions, yielded the desired pyrrole benzylamide, **13Aa**, in 99% purity. In addition, 3-aminopyrrole-2,5-dimethylesters, **11**, were prepared from 2-trichloromethyl ketone resin **10** by simultaneous haloform reaction and resin cleavage using 1000 mol % of 0.3 M NaOMe in THF/MeOH (4:1) for 6 h at room temperature.

Acylation at the 2-position was initially assumed on the basis of the general reactivity of pyrrole; however, 2-acyl pyrroles have been reported to alter the selectivity of electrophilic addition on pyrrole.[42−45] Confirmation of regio-

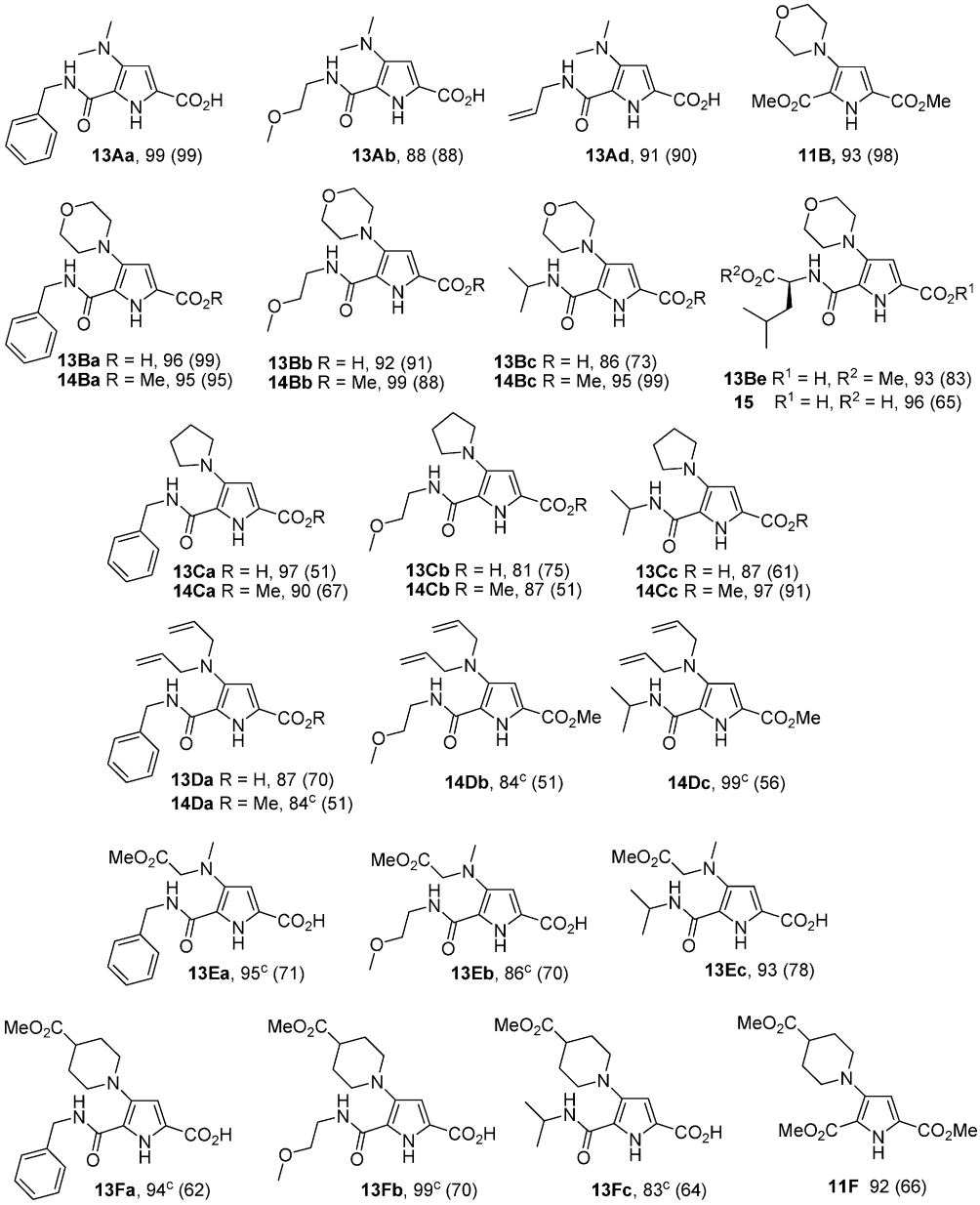


Figure 4. 3-Aminopyrrole-2,5-dicarboxylate analogues. The % purity is given as determined by reversed-phase HPLC with monitoring at 214 nm, and the % yield is based on the PhFH recovered from **9**. Superscript c denotes the purity of the product after acid−base extraction.

selectivity at the 2-position was obtained by 1D NOE experiments on 2-allylcarbamoyl-3-(dimethylamino)-1*H*-pyrrole-5-carboxylic acid **13Ad** (Figure 3). Experiments in which saturation of the signals of the pyrrole nitrogen proton (12.62 ppm) and the pyrrole aromatic proton (7.22 ppm) caused, respectively, the enhancement of the signal of the amido proton (8.84 ppm) and the methyl singlet (3.11 ppm) for the dimethyl amino group indicated 2-position acylation.

Analysis of the LCMS trace of 2-*N*′-methoxyethylcarbamoyl-3-dimethylaminopyrrole-5-carboxylic acid **13Ab** indicated the presence of an additional peak with a mass of 356.2 corresponding to product from double acylation of pyrrole. Isolation of this second peak by preparative HPLC provided sufficient material for ^{1}H NMR analysis. The disappearance of the 4-position proton at 7.26 ppm, the appearance of a second amide proton at 11.34 ppm, and the doubling of the integration for the methoxyethyl protons in the ^{1}H NMR spectrum were all consistent with the formation of 2,4-di(*N*′-methoxyethylcarbamoyl)-3-dimethylaminopyrrole-5-carboxylic acid **17** (Figure 3). Although the formation of 3-aminopyrrole-2,4,5-tricarboxylate **17** demonstrates the potential for double acylation of aminopyrroles in reactions with excess Cl_3CCOCl, this reaction has yet to be pursued.

Cleavage of the products from the resin was effected using two different procedures to introduce two different units of diversity at the 5-position. Carboxylic acids, **13**, were obtained by treating the **12** resins twice with TFA/CH_2Cl_2 (1:3) at room temperature for 30 min. The **13** acids were typically isolated in pure form by filtration of the resin and evaporation of the filtrate. The **13C** acids were triturated with a pentane/diethyl ether solution (1:1) to remove minor impurities detected by ^{1}H NMR spectroscopy between 0 and 2 ppm. The LCMS traces of the **13E** and **13F** acids showed the presence of PhFH, which was removed by acid−base extraction. In this manner, pyrrole acids, **13**, of high purity (81−99%) were obtained in yields of 51−99% (Figure 4).

Methyl esters, **14**, were produced by submitting the **12** resins to 1000 mol % of 0.3 M NaOMe in THF/MeOH (4:1) for 24 h at room temperature twice. The **14** esters were typically isolated in pure form by filtration, washing of the resin with EtOAc, and partitioning the filtrate between EtOAc and a saturated NH_4Cl aqueous solution. When water was used to partition the filtrate instead of a saturated NH_4Cl solution, methyl ester hydrolysis occurred to produce the **13** acids as well as diacid **15**, which was isolated in a 65% yield and 96% purity by acidification of the aqueous layer to pH 6 and extraction with EtOAc. To remove minor impurities detected by ^{1}H NMR spectroscopy between 0 and 2 ppm, ester **14Ca** was triturated with a pentane/diethyl ether solution (1:1), and esters **14Cb** and **14Cc** were dissolved in Et_2O and filtered. The LCMS traces of the **14D** esters showed the presence of PhFH, which was removed by acid−base extraction. In this way, pyrrole esters of high purity (84−99%) were obtained in yields of 51−99% (Figure 4).

Conclusions

The first polymer-supported synthesis of 3-aminopyrrole-2,5-dicarboxylate has been accomplished using (2*S*,4*R*)-hydroxy-*N*-(PhF)proline **5** and Wang resin. Three units of diversity were added to the pyrrole ring, first by the exposure of 4-oxo-*N*-(PhF)prolyl resin **8** to secondary amines, second by the haloform reaction of 2-trichloroacetyl-3-amino-1*H*-pyrrole-5-carboxylate resin **10**, and third by carboxylate cleavage with TFA or sodium methoxide. A library composed of twenty-nine 3-aminopyrrole-2,5-dicarboxylate analogues was prepared in 81−99% purities and 51−99% yields. More diversity may be achieved by pyrrole nitrogen alkylation, electrophilic substitution at the pyrrole 4-position, and further modifications of the carboxylate groups. This new methodology offers effective means for the facile regioselective diversification of pyrrole to produce pure analogues. The potential of this protocol is now being explored for preparing larger libraries of structurally diverse pyrroles that may have beneficial uses in fields such as chemical biology, materials science, and medicine.

Experimental Section

General. For anhydrous conditions, the glassware was flame-dried and the reaction was performed under a positive pressure of argon. Anhydrous CH_2Cl_2 (DCM), tetrahydrofuran (THF), and *N*,*N*-dimethylformamide (DMF) were obtained by passage through solvent filtration systems (GlassContour, Irvine, CA). Shaking at room temperature was performed on a reciprocating shaker (SK-300 Jeio Tech). Melting points are uncorrected. Mass spectral data, HRMS/LRMS (EI and FAB), were obtained by the Centre Régional de Spectrométrie de Masse de l′Université de Montréal. Unless otherwise noted, ^{1}H NMR (300/400 MHz) and ^{13}C NMR (75/100 MHz) spectra were recorded in DMSO-d_6. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane ($(CH_3)_4Si$) standard, residual DMSO (δ 2.50 and 39.5), residual MeOH (δ 3.31 and 49.0), or residual $CHCl_3$ (δ 7.27 and 77.2)); coupling constants (*J*) are reported in hertz (Hz). The chemical shifts of the PhF aromatic carbons are not reported in the ^{13}C NMR spectra. HPLC analyses were performed on a Alltech Prevail C18 (5 μm, 250 × 4.6 mm) analytical reversed-phase column using a flow rate of 0.5 mL/min and gradients of 80/20 to 20/80 eluants A/B over 20 min (method A), 95/5 to 60/40 eluants A/B over 20 min (method B), on a Betasil C18 (5 μm, 150 × 4.6 mm) analytical reversed-phase column using a flow rate of 0.5 mL/min and gradients of 80/20 to 20/80 eluants A/B over 10 min (method C), 95/5 to 60/40 eluants A/B over 10 min (method D), or on a YMC C18 (5 μm, 50 × 4.6 mm) analytical reversed-phase column using a flow rate of 0.5 mL/min, and gradients of 80/20 to 20/80 eluants A/B over 5 min (method E), 95/5 to 60/40 eluants A/B over 5 min (method F), in which eluant A is H_2O/0.1% TFA and B is CH_3CN/0.1% TFA. Retention times (R_t) are reported as follows: R_t (min) and elution conditions. HPLC semi-preparative purification was performed on an Alltech Prevail C18 (5 μm, 250 × 22 mm) semipreparative column using a flow rate of 15 mL/min and a gradient of 95/5 to 60/40 eluants A/B over 20 min. Analytical thin-layer chromatography (TLC) was performed by using glass-backed silica gel plates coated with a 0.2 mm thickness of silica gel. Flash column chromatography[46] was performed with a 230−400 mesh silica gel. Infrared spectra were taken on a PerkinElmer Spectrum One apparatus. Unless otherwise noted, resins were swollen in the specified solvent for 1 h prior to the reaction and washed for 2 min with each solvent in polypropylene tubes equipped with polyethylene frits and polypropylene stoppers and caps. Glassware was coated with Aqua Sil film and dried 1 h in the oven at 120 °C before being used for solid-phase reactions.

Acids **13A**, **13B**, and **13Da** and esters **11** and **14B** were isolated in pure form (>86% purity) after evaporation of the filtrate. To remove the minor impurities detected by ^{1}H NMR spectroscopy, acids **13C** and ester **14Ca** were triturated with a pentane/Et_2O solution (1:1) and evaporated, and esters **14Cb** and **14Cc** were dissolved in Et_2O, filtered, and evaporated. Purification of acids **13E** and **13F** and the **14D** esters from PhFH impurity was performed by an acid−base extraction. For example, ester **14Dc** (30 mg, 72% purity) was dissolved in 10 mL of EtOAc and extracted with portions of a 10% HCl solution (3 × 15 mL). The aqueous phases were combined, adjusted to pH 7 with a saturated solution of $NaHCO_3$, and extracted with portions of EtOAc (3 × 20 mL). The organic layers were combined, washed with a saturated NaCl solution, dried on Na_2SO_4, and evaporated to dryness to give ester **14Dc** as a clean product (20 mg, 99% purity).

(2*S*,4*R*)-4-Hydroxy-*N*-1-(PhF)proline (5). A solution of (2*S*,4*R*)-4-hydroxy-*N*-(PhF)proline methyl ester (**4**, 5.0 g, 13.0 mmol, prepared according to ref 40) and LiOH (3.1 g, 130.0 mmol) in 250 mL of a 3:2:1 mixture of THF/MeOH/H_2O was stirred for 12 h under reflux. After the mixture was cooled to room temperature, the resulting solution was diluted with 250 mL of 10% aqueous KOH, washed with 100 mL of CH_2Cl_2, acidified with 10% HCl, and extracted 3-fold with CH_2Cl_2. Drying on Na_2SO_4 and the removal of the solvent yielded crude **5** which was crystallized from EtOAc/hexanes. Yield: 87%. White crystals. mp: 121−124 °C. $[\alpha]_D^{20}$ 170.0° (*c* 0.5, CH_3OH). IR (KBr, cm^{-1}): 3380

(OH), 1720 (C═O). ^{1}H NMR (CD_3OD): δ 7.80−7.16 (m, 13H), 4.41 (pent, 1H, J = 7.8 Hz), 3.48 (dd, 1H, J = 9.3, 6.1 Hz), 3.28 (dd, 1H, J = 9.8, 2.7 Hz), 2.78 (dd, 1H, J = 9.2, 7.8 Hz), 2.00 (m, 1H), 1.72 (m, 1H). ^{13}C NMR (CD_3OD): δ 177.8, 77.3, 68.9, 60.5, 56.3, 39.2. HRMS: calcd for [M + H$^+$] $C_{24}H_{22}NO_3$, 372.1600; found, 372.1588.

(2*S*,4*R*)-4-Hydroxy-*N*-(PhF)proline resin (7). A solution of acid **5** (1.0 g, 2.7 mmol) in 10 mL of MeOH was treated with 1.0 mL of H_2O, titrated with 20% Cs_2CO_3 to pH 7, and evaporated to dryness. Wang bromide (3.0 g, 0.6 mmol/g), purchased from Novabiochem or prepared from Wang resin[41] purchased from Advanced ChemTech, Inc., was swollen in a 60 mL polypropylene tube with a polyethylene frit and stopper using 20 mL of dry DMF, washed with 20 mL of dry DMF (×2), transferred to a 100 mL tricol round-bottom flask, treated with a solution of cesium salt **6** (1.36 g, 2.7 mmol) in dry DMF (30 mL), and heated in an oil bath with overhead stirring at 60 °C for 48 h. The resin was placed into a 60 mL polypropylene tube, equipped with a polyethylene frit, washed sequentially with 20 mL solutions of CH_2Cl_2, EtOH, H_2O, CH_2Cl_2, EtOH, H_2O, EtOH (×2), and CH_2Cl_2 (×3). The beige resin was dried in vacuo and usually stored in a desiccator under vacuum or under argon in the refrigerator. IR (KBr, cm^{-1}): 3438(OH), 1731(C═O). The collected filtrates were evaporated, dissolved in EtOAc, and washed with 1 M NaH_2PO_4. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried on Na_2SO_4, filtered, and evaporated. Crystallization of the residue from EtOAc/hexanes yielded (2*S*,4*R*)-4-hydroxy-*N*-(PhF)proline **5** (0.23 g, 0.63 mmol).

4-Oxo-*N*-(PhF)prolyl resin (8). Hydroxyproline resin **7** (3.52 g, 1.80 mmol) was swollen in a 60 mL polypropylene tube with a polyethylene frit and stopper using 20 mL of CH_2Cl_2, filtered, washed with 20 mL of CH_2Cl_2 (×2), transferred to a 100 mL tricol equipped with an overhead stirrer, suspended in 35 mL of CH_2Cl_2, and cooled to −78 °C. In a separate 50 mL round-bottomed flask, 9.0 mmol (0.78 mL) of freshly distilled $(COCl)_2$ was added dropwise to a solution of 18.0 mmol (1.28 mL) of dry DMSO in 20 mL of dry CH_2Cl_2 at −78 °C, stirred for 30 min, and cannulated to the resin suspension. The resin mixture was agitated for 4 h at −78 °C, treated with distilled and dried Et_3N (3.76 mL, 27.0 mmol) dropwise, and stirred for 1 h at −78 °C. After it was warmed to room temperature, the resin was washed sequentially with 20 mL volumes of CH_2Cl_2 (×2), EtOH (×2), CH_2Cl_2 (×2), EtOH (×2), and CH_2Cl_2 (×2). The beige resin was dried in vacuo and usually stored in a desiccator under vacuum or under argon in the refrigerator. IR (KBr, cm^{-1}): 1752 and 1726 (C═O).

General Procedure A: 4-Amino-1*H*-pyrrole-2-carboxylate Resins (9). Resin **8** (3.0 g, 1.50 mmol) was loaded into a 60 mL polypropylene tube equipped with a polyethylene frit and stopper, swollen in 20 mL of dry THF, filtered, washed with 20 mL of dry THF (×2), transferred to a 100 mL tricol equipped with an overhead stirrer, and swollen in 30 mL of dry THF. The resin suspension was treated with the respective amine (800 mol %) and dry *p*-TsOH (10 mol %); for the amine hydrochloride salts (800 mol %), Et_3N (780 mol %) was used instead of *p*-TsOH. The resulting mixture was stirred for 18 h at 50 °C in an oil bath, cooled, transferred into a 60 mL polypropylene tube equipped with a polyethylene frit, filtered, and washed sequentially with 20 mL volumes of THF, CH_2Cl_2, EtOH, H_2O, CH_2Cl_2, EtOH, H_2O, EtOH (×2), and CH_2Cl_2 (×3). The brown resin was dried in vacuo and stored in the refrigerator under argon. IR (KBr, cm^{-1}): 1695 (C═O). Evaporation of the filtrate, followed by chromatographic purification (90:10 hexanes/EtOAc, R_f = 0.7) yielded PhFH (mp 148 °C, litt.[47] mp 147−148 °C), which was used to quantify the loading of the pyrrole.

General Procedure B: 2-Trichloroacetyl-3-amino-1*H*-pyrrole-5-carboxylate Resin (10). Resin **9** (900 mg, 0.45 mmol) was placed into a 12 mL polypropylene tube equipped with a polyethylene frit and stopper, swollen in 5 mL of dry CH_2Cl_2, filtered, washed with 5 mL of dry CH_2Cl_2(×2), suspended in 4 mL of dry CH_2Cl_2, treated with Et_3N (0.20 mL, 1.40 mmol) and trichloroacetyl chloride (0.17 mL, 1.49 mmol), and shaken at room temperature for 4 h. The resin was filtered, washed sequentially with 5 mL volumes of CH_2Cl_2 (×2) and THF (×2), and used directly in the next step.

General Procedure C: Dimethyl-3-Aminopyrrole-2,5-dicarboxylates (11). Trichloroacetyl resin **10** (300 mg, 0.15 mmol) in the same 12 mL polypropylene tube was swollen in 3 mL of dry THF, treated with 0.3 M NaOMe in THF/MeOH (4:1, 3.0 mL), and shaken at room temperature for 6 h. The resin was filtered and washed with 5 mL volumes of THF (×2) into a separating funnel containing 5 mL of a saturated NH_4Cl solution. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried on Na_2SO_4, filtered, and evaporated to yield the **11** diesters, which were **s**tored in the refrigerator under argon.

Dimethyl-3-morpholino-1*H*-pyrrole-2,5-dicarboxylate (11B). Yield: 98%. Yellow solid. mp: 87 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 11.97 (s, 1H), 6.51 (s, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.69 (t, 4H, J = 4.6 Hz), 2.98 (t, 4H, J = 4.6 Hz). ^{13}C NMR (DMSO-d_6): δ 160.1, 159.5, 145.5, 123.6, 114.4, 104.9, 66.1, 51.8, 51.6, 51.1. HRMS: calcd for [M + H$^+$] $C_{12}H_{17}N_2O_5$, 269.1132; found, 269.1126. R_t: 8.51, method C; 6.19, method F.

Dimethyl-3-(4-methyloxycarbonylpiperidino)amino-1*H*-pyrrole-2,5-dicarboxylate (11F). Yield: 66%. Light beige solid. mp: 82 °C (decomp). Banana odor. ^{1}H NMR (DMSO-d_6): δ 11.98 (s, 1H), 6.49 (s, 1H), 3.78 (s, 3H), 3. 75 (s, 3H), 3.63 (s, 3H), 3.51 (m, 2H), 2.63 (t, 2H, J = 11.0 Hz), 2.47 (m, 1H), 1.87 (m, 2H), 1.71 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 174.9, 160.1, 159.5, 145.9, 123.6, 114.5, 105.3, 51.7, 51.5, 51.4, 42.9, 37.6, 24.5. HRMS: calcd for [M + H$^+$] $C_{15}H_{21}N_2O_6$, 325.1394; found, 325.1395. R_t: 7.77, method C; 3.58, method E.

General Procedure D: 2-N′-substituted Carbamoyl-3-aminopyrrole-5-carboxylate Resin (12). Trichloroacetyl resin **10** (900 mg, 0.41 mmol), in the same 12 mL polypropylene tube, was swollen in 4 mL of dry THF, treated with the specified amine (600 mol %), and shaken at room temperature for 1 h. The resin was filtered, washed sequentially with 5 mL volumes of THF (×2), CH_2Cl_2 (×2), EtOH

(×2), and CH_2Cl_2 (×2), dried in vacuo, and stored in the refrigerator under argon.

General Procedure E: 2-Carbamoyl-3-aminopyrrole-5-carboxylic Acid (13). 5-Carboxylate resin **12** (300 mg, 0.15 mmol), in a 12 mL polypropylene tube, was swollen in 3 mL of dry CH_2Cl_2, filtered, washed with 3 mL of dry CH_2Cl_2 (×2), treated with a 25% v/v solution of TFA in CH_2Cl_2 (3 mL), and shaken for 30 min. The resin was filtered, washed with CH_2Cl_2(×2), and treated again with 25% TFA in CH_2Cl_2 for an additional 30 min. The resin was filtered and washed with CH_2Cl_2 (×2). The combined filtrates and washings were evaporated under reduced pressure and triturated with a pentane/Et_2O solution (1:1) to yield the **13** acids.

2-Benzylcarbamoyl-3-(dimethylamino)-1*H*-pyrrole-5-carboxylic Acid (13Aa). Yield 99%. Purple solid. mp: 104 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 12.71 (s, 1H), 9.17 (t, 1H, J = 5.6 Hz), 7.37 (d, 4H, J = 4.2 Hz), 7.30 (quint, 1H, J = 4.2 Hz), 7.26 (d, 1H, J = 2.4 Hz), 4.52 (d, 2H, J = 5.5 Hz), 3.16 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 160.9, 159.3, 138.2, 133.1, 128.6, 127.8, 127.4, 124.3, 119.1, 107.4, 47.1, 42.5. HRMS: calcd for [M + H$^+$] $C_{15}H_{18}N_3O_3$, 288.1343; found, 288.1349. R_t: 13.87, method D.

2-Methoxyethylamido-3-(dimethylamino)-1*H*-pyrrole-5-carboxylic Acid (13Ab). Yield 88%. Reddish-purple solid. mp: 107 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 12.79 (s, 1H), 8.86 (s, 1H), 7.26 (d, 1H, J = 2.2 Hz), 3.48 (s, 4H), 3.29 (s, 3H), 3.15 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 160.9, 159.4, 132.8, 124.2, 119.1, 107.3, 70.3, 58.0, 47.1, 38.6. IR (KBr, cm^{-1}) on resin: 3443 large (N−H), 1709, 1652 (C═O). HRMS: calcd for [M + H$^+$] $C_{11}H_{18}N_3O_4$, 256.1292; found, 256.1294. R_t: 9.61, method D.

2-Allylcarbamoyl-3-(dimethylamino)-1*H*-pyrrole-5-carboxylic Acid (13Ad). Yield: 90%. Brown solid. mp: 112 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 12.63 (s, 1H), 8.84 (t, 1H, J = 5.4 Hz), 7.22 (d, 1H, J = 1.7 Hz), 5.87−5.94 (m, 1H), 5.27 (dd, 1H, J = 17.2, 1.5 Hz), 5.17 (dd, 1H, J = 10.3, 1.4 Hz), 3.96 (t, 2H, J = 5.4 Hz), 3.11 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 160.9, 159.2, 134.3, 133.7, 124.1, 119.3, 116.3, 107.4, 47.0, 41.0. HRMS: calcd for [M + H$^+$] $C_{11}H_{16}N_3O_3$, 238.1186; found, 238.1191. R_t: 10.60, method D.

2-Benzylcarbamoyl-3-morpholino-1*H*-pyrrole-5-carboxylic Acid (13Ba). Yield 99%. Purple solid. mp: 112 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 11.95 (s, 1H), 9.01 (s, 1H), 7.36−7.24 (m, 5H), 6.85 (s, 1H), 4.50 (s, 2H), 3.60 (s, 4H), 2.96 (s, 4H). ^{13}C NMR (DMSO-d_6): δ 161.2, 159.3, 138.9, 138.9, 128.5, 127.7, 127.2, 123.4, 120.1, 107.8, 65.8, 53.8, 42.3. HRMS: calcd for [M + H$^+$] $C_{17}H_{20}N_3O_4$, 330.1448; found, 330.1447. R_t: 10.84, method C.

2-Methoxyethylcarbamoyl-3-morpholino-1*H*-pyrrole-5-carboxylic Acid (13Bb). Yield: 91%. Purple solid. mp: 112 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 11.68 (s, 1H), 8.85 (s, 1H), 6.81 (s, 1H), 3.74 (t, 4H, J = 4.6 Hz), 3.47 (s, 4H), 3.31 (s, 3H), 2.85 (t, 4H, J = 4.4 Hz). ^{13}C NMR (DMSO-d_6): δ 170.6, 161.3, 139.7, 123.4, 121.6, 108.0, 70.7, 66.4, 57.9, 53.8, 38.1. HRMS: calcd for [M + H$^+$] $C_{13}H_{20}N_3O_5$, 298.1398; found, 298.1400. R_t: 8.01, method C.

2-Isopropylcarbamoyl-3-morpholino-1*H*-pyrrole-5-carboxylic Acid (13Bc). Yield: 73%. Purple solid. mp: 110 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 11.62 (s, 1H), 8.53 (d, 1H, J = 7.5 Hz), 6.75 (s, 1H), 4.01 (sept, 1H, J = 6.7 Hz), 3.71 (t, 4H, J = 4.2 Hz), 2.84 (t, 4H, J = 4.3 Hz), 1.17 (d, 6H, J = 6.5 Hz). ^{13}C NMR (DMSO-d_6): δ 161.4, 158.8, 139.9, 123.1, 121.4, 107.8, 66.6, 53.5, 40.3, 22.7. HRMS: calcd for [M + H$^+$] $C_{13}H_{20}N_3O_4$, 282.1448; found, 282.1450. R_t: 9.34, method C.

2-[(1′*S*)-Methyloxycarbonyl-3′-methylbutyl]carbamoyl-3-morpholino-1*H*-pyrrole-5-carboxylic Acid (13Be). Yield: 83%. Purple solid. mp: 112 °C (decomp). $[\alpha]_D^{23}$ 6.5° (c 0.2, DMSO). ^{1}H NMR (DMSO-d_6): δ 11.80 (s, 1H), 9.08 (d, 1H, J = 8.1 Hz), 6.78 (d, 1H, J = 2.5 Hz), 4.56 (q, 1H, J = 7.4 Hz), 3.70−3.75 (m, 4H), 3.65 (s, 3H), 2.80−2.90 (m, 4H), 1.64 (m, 3H), 0.90 (t, 6H, J = 6.7 Hz). ^{13}C NMR (DMSO-d_6): δ 173.0, 161.2, 159.3, 139.8, 123.8, 120.5, 107.9, 66.2, 53.7, 52.1, 49.9, 40.7, 24.5, 22.7, 21.6. HRMS: calcd for [M + H$^+$] $C_{17}H_{26}N_3O_6$, 368.1816; found, 368.1820. R_t: 11.74, method C.

2-Benzylcarbamoyl-3-pyrrolidino-1*H*-pyrrole-5-carboxylic Acid (13Ca). Yield: 51%. Brown powder. ^{1}H NMR (DMSO-d_6): δ 11.91 (s, 1H), 8.89 (s, 1H), 7.35−7.27 (m, 5H), 6.75 (s, 1H), 4.48 (d, 2H, J = 5.5 Hz), 3.23 (s, 4H), 1.83 (s, 4H). ^{13}C NMR (DMSO-d_6): 161.3, 159.5, 139.0, 139.0, 128.5, 127.6, 127.1, 123.2, 119.2, 106.3, 54.7, 42.3, 23.9. HRMS: calcd for [M + H$^+$] $C_{17}H_{20}N_3O_3$, 314.1499; found, 314.1499. R_t: 4.24, method E.

2-Methoxyethylcarbamoyl-3-pyrrolidino-1*H*-pyrrole-5-carboxylic Acid (13Cb). Yield: 75%. Brown powder. ^{1}H NMR (DMSO-d_6): δ 12.51 (s, 1H), 8.76 (s, 1H), 7.04 (s, 1H), 3.61 (s, 4H), 3.43 (s, 4H), 3.24 (s, 3H), 2.06 (s, 4H). ^{13}C NMR (DMSO-d_6): 161.8, 160.3, 130.6, 124.8, 120.9, 108.3, 71.0, 59.1, 58.9, 38.8, 23.9. HRMS: calcd for [M + H$^+$] $C_{13}H_{20}N_3O_4$, 282.1448; found, 282.1445. R_t: 18.68, method B; 4.48, method F.

2-Isopropylcarbamoyl-3-pyrrolidino-1*H*-pyrrole-5-carboxylic Acid (13Cc). Yield: 61%. Brown powder. ^{1}H NMR (DMSO-d_6): δ 11.40 (s, 1H), 8.16 (d, 1H, J = 7.3 Hz), 6.53 (d, 1H, J = 2.3 Hz), 4.00 (sept, 1H, J = 6.7 Hz), 3.01 (s, 4H), 1.84 (s, 4H), 1.15 (d, 6H, J = 6.5 Hz). ^{13}C NMR (DMSO-d_6): 161.5, 159.0, 138.9, 122.3, 119.2, 105.6, 52.7, 40.3, 24.2, 22.6. HRMS: calcd for [M + H$^+$] $C_{13}H_{20}N_3O_3$, 266.1499; found, 266.1496. R_t: 5.01, method F.

2-Benzylcabamoyl-3-diallylamino-1*H*-pyrrole-5-carboxylic Acid (13Da). Yield: 70%. Light brown powder. ^{1}H NMR (DMSO-d_6): δ 11.55 (s, 1H), 9.19 (t, 1H, J = 6.0 Hz), 7.23−7.33 (m, 5H), 6.78 (d, 1H, J = 2.5 Hz), 5.67 (m, 2H), 5.04 (m, 4H), 4.50 (d, 2H, J = 5.9 Hz), 3.45 (d, 4H, J = 6.4 Hz). ^{13}C NMR (DMSO-d_6): δ 161.3, 159.7, 139.3, 134.6, 128.4, 128.0, 127.3, 127.0, 123.4, 123.3, 118.4, 110.2, 58.3, 41.9. HRMS: calcd for [M + H$^+$] $C_{19}H_{22}N_3O_5$, 340.1656; found, 340.1658. R_t: 12.60, method C.

2-Benzylcarbamoyl-3-(N-methoxycarbonylmethyl-*N*-methyl)amino-1*H*-pyrrole-5-carboxylic Acid (13Ea). Yield: 71%. Brown solid. mp: 95 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 11.58 (s, 1H), 9.09 (t, 1H, J = 5.8 Hz), 7.35−7.25 (m, 5H), 6.73 (s, 1H), 4.48 (d, 2H, J = 6.0 Hz), 3.88 (s, 2H), 3.52 (s, 3H), 2.68 (s, 3H). ^{13}C NMR (DMSO-d_6):

170.9, 161.3, 159.6, 140.2, 139.4, 128.3, 127.2, 126.8, 123.1, 120.3, 108.3, 58.0, 51.4, 43.2, 41.9. HRMS: calcd for [M + H^+] $C_{17}H_{20}N_3O_5$, 346.1398; found, 346.1399. R_t: 19.95, method A.

2-Methoxyethylcarbamoyl-3-(*N*-methoxycarbonylmethyl-*N*-methyl)amino-1*H*-pyrrole-5-carboxylic Acid (13Eb). Yield: 70%. Brown solid. mp: 92 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 12.13 (s, 1H), 8.94 (s, 1H), 6.94 (s, 1H), 4.17 (s, 2H), 3.63 (s, 3H), 3.45 (s, 4H), 3.27 (s, 3H), 2.88 (s, 3H). ^{13}C NMR (DMSO-d_6): 170.7, 161.4, 159.6, 139.7, 122.9, 120.2, 108.4, 70.7, 58.0, 51.5, 43.3, 38.5, 38.2. HRMS: calcd for [M + H^+] $C_{13}H_{20}N_3O_6$, 314.1347; found, 314.1339. R_t: 14.89, method A.

2-Isopropylcarbamoyl-3-(*N*-methoxycarbonylmethyl-*N*-methyl)amino-1*H*-pyrrole-5-carboxylic Acid (13Ec). Yield: 78%. Purple solid. mp: 107 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 11.49 (s, 1H), 8.54 (d, 1H, J = 7.6 Hz), 6.73 (s, 1H), 4.03 (sept, 1H, J = 6.8 Hz), 3.75 (s, 2H), 3.63 (s, 3H), 2.66 (s, 3H), 1.15 (d, 6H, J = 6.6 Hz). ^{13}C NMR (DMSO-d_6): 170.9, 161.3, 158.7, 139.7, 122.7, 120.9, 108.4, 70.7, 58.0, 51.5, 43.3, 43.0, 22.5. HRMS: calcd for [M + H^+] $C_{13}H_{20}N_3O_5$, 298.1398; found, 298.1401. R_t: 10.50, method C.

2-Benzylcarbamoyl-3-(4-methyloxycarbonylpiperidino)-amino-1*H*-pyrrole-5-carboxylic Acid (13Fa). Yield: 62%. Beige solid. mp: 90 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 12.38−11.77 (br s, 1H), 9.07 (t, 1H, J = 5.5 Hz), 7.37 (d, 4H, J = 4.2 Hz), 7.28 (quint, 1H, J = 4.3 Hz), 6.89 (s, 1H), 4.51 (d, 2H, J = 5.5 Hz), 3.63 (s, 3H), 3.18 (br s, 2H), 2.95 (br s, 2H), 2.54 (s, 1H), 1.91 (br s, 2H), 1.68 (br s, 2H). ^{13}C NMR (DMSO-d_6): δ 174.1, 161.1, 159.3, 138.7, 138.7, 128.6, 127.6, 127.2, 123.6, 120.8, 107.8, 53.8, 51.7, 42.3, 39.9, 28.2. HRMS: calcd for [M + H^+] $C_{20}H_{24}N_3O_5$, 386.1711; found, 386.1702. R_t: 19.95, method A.

2-Methoxyethylcarbamoyl-3-(4-methyloxycarbonyl-piperidino)amino-1*H*-pyrrole-5-carboxylic Acid (13Fb). Yield: 70%. Beige solid. mp: 150 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 11.56 (s, 1H), 8.93 (s, 1H), 6.75 (s, 1H), 3.64 (s, 3H), 3.46 (s, 4H), 3.30 (s, 3H), 2.95 (m, 2H), 2.70 (m, 2H), 2.45 (m, 1H), 1.92 (m, 2H), 1.78 (m, 2H). ^{13}C NMR (DMSO-d_6): 174.8, 161.3, 159.6, 140.3, 123.2, 121.8, 108.1, 70.7, 58.0, 53.3, 51.5, 39.6, 38.1, 28.3. HRMS: calcd for [M + H^+] $C_{16}H_{24}N_3O_6$, 354.1660; found, 354.1663. R_t: 8.65, method C.

2-Isopropylamido-3-(4-methyloxycarbonylpiperidino)-amino-1*H*-pyrrole-5-carboxylic Acid (13Fc). Yield: 64%. Brown solid. mp: 130 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 11.55 (s, 1H), 8.60 (d, 1H, J = 7.4 Hz), 6.72 (s, 1H), 4.04 (quint, 1H, J = 6.6 Hz), 3.62 (s, 3H), 2.97 (m, 2H), 2.69 (m, 2H), 2.45 (m, 1H), 1.97 (m, 2H), 1.74 (m, 2H), 1.18 (d, 6H, J = 6.5 Hz). ^{13}C NMR (DMSO-d_6): 174.7, 161.3, 158.8, 140.2, 123.0, 121.6, 107.9, 53.1, 51.6, 43.0, 37.6, 28.6, 22.8. HRMS: calcd for [M + H^+] $C_{16}H_{24}N_3O_5$, 338.1711; found, 338.1701. R_t: 16.59, method A; 9.08, method C; 4.47, method E.

General Procedure F: 2-Carbamoyl-3-aminopyrrole-5-carboxylate (14). Carboxylate resin **12** (300 mg, 0.15 mmol) in a 12 mL polypropylene tube was swollen in 3 mL of dry THF, filtered, washed with 3 mL of dry THF (×2), treated with 0.3 M NaOMe in THF/MeOH (4:1, 3 mL), and shaken at room temperature for 24 h, twice. The resin was filtered and washed with 5 mL volumes of THF (×2), and the filtrate and washings were collected in a separating funnel containing a saturated NH_4Cl solution. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried on Na_2SO_4, filtered, and evaporated to yield the **14** methyl esters, which were stored in the fridge under argon.

Methyl-2-benzylcarbamoyl-3-morpholino-1*H*-pyrrole-5-carboxylate (14Ba). Yield: 95%. Beige solid. mp: 208 °C. ^{1}H NMR (DMSO-d_6): δ 12.05 (s, 1H), 9.00 (s, 1H), 7.36 (m, 5H), 6.83 (s, 1H), 4.49 (d, 2H, J = 5.2 Hz), 3.76 (s, 3H), 3.50 (s, 4H), 2.79 (s, 4H). ^{13}C NMR (DMSO-d_6): δ 160.3, 159.4, 140.3, 139.0, 128.5, 127.7, 127.2, 122.1, 121.8, 108.2, 66.2, 53.5, 51.5, 42.3. HRMS: calcd for [M + H^+] $C_{18}H_{22}N_3O_4$, 344.1605; found, 344.1607. R_t: 12.68, method C.

Methyl-2-methoxyethylcarbamoyl-3-morpholino-1*H*-pyrrole-5-carboxylate (14Bb). Yield: 88%. Yellow solid. mp: 121 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 11.96 (s, 1H), 8.87 (s, 1H), 6.85 (s, 1H), 3.75 (s, 3H), 3.72 (t, 4H, J = 4.3 Hz), 3.47 (s, 4H), 3.35 (s, 3H), 2.81 (t, 4H, J = 4.4 Hz). ^{13}C NMR (DMSO-d_6): δ 160.2, 159.4, 139.9, 122.3, 122.1, 108.4, 70.7, 66.4, 58.0, 53.7, 51.4, 38.3. HRMS: calcd for [M + H^+] $C_{14}H_{22}N_3O_5$, 312.1554; found, 312.1551. R_t: 9.81, method C.

Methyl-2-isopropylcarbamoyl-3-morpholino-1*H*-pyrrole-5-carboxylate (14Bc). Yield: 99%. Beige solid. mp: 150 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 11.89 (s, 1H), 8.56 (d, 1H, J = 7.7 Hz), 6.85 (s, 1H), 4.03 (sept, 1H, J = 6.7 Hz), 3.76 (s, 3H), 3.72 (t, 4H, J = 4.4 Hz), 2.84 (t, 4H, J = 4.5 Hz), 1.19 (d, 6H, J = 6.5 Hz). ^{13}C NMR (DMSO-d_6): δ 160.3, 158.6, 139.8, 122.1, 121.8, 108.1, 66.6, 53.5, 51.4, 40.3, 22.7. HRMS: calcd for [M + H^+] $C_{14}H_{22}N_3O_4$, 296.1605; found, 296.1600. R_t: 4.90, method E.

Methyl-2-benzylcarbamoyl-3-pyrrolidino-1*H*-pyrrole-5-carboxylate (14Ca). Yield: 67%. Gray solid. Insoluble in Et_2O. mp: 152 °C. ^{1}H NMR (DMSO-d_6): δ 11.70 (s, 1H), 8.76 (t, 1H, J = 5.0 Hz), 7.34−7.26 (m, 5H), 6.56 (s, 1H), 4.46 (d, 2H, J = 5.6 Hz), 3.77 (s, 3H), 2.99 (s, 4H), 1.76 (s, 4H). ^{13}C NMR (DMSO-d_6): δ 160.4, 159.7, 139.4, 139.4, 128.4, 127.4, 126.9, 121.4, 119.4, 105.8, 52.8, 51.4, 42.2, 24.2. HRMS: calcd for [M + H^+] $C_{18}H_{22}N_3O_3$, 328.1656; found, 328.1656. R_t: 4.70, method E.

Methyl-2-methoxyethylcarbamoyl-3-pyrrolidino-1*H*-pyrrole-5-carboxylate (14Cb). Yield: 51%. Isolated as an orange gum. ^{1}H NMR (DMSO-d_6): δ 11.71 (s, 1H), 8.58 (s, 1H), 6.67 (d, 1H, J = 2.4 Hz), 3.76 (s, 3H), 3.43 (br s, 4H), 3.28 (s, 3H), 2.98 (t, 4H, J = 6.0 Hz), 1.85 (t, 4H, J = 6.3 Hz). ^{13}C NMR (DMSO-d_6): 160.4, 159.7, 138.7, 121.5, 120.8, 106.5, 70.8, 58.0, 53.2, 51.4, 38.1, 24.1. HRMS: calcd for [M + H^+] $C_{14}H_{22}N_3O_4$, 296.1605; found, 296.1597. R_t: 5.62, method F.

Methyl-2-isopropylcarbamoyl-3-pyrrolidino-1*H*-pyrrole-5-carboxylate (14Cc). Yield: 91%. Yellow solid. mp: 143 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 11.66 (s, 1H), 8.21 (d, 1H, J = 7.4 Hz), 4.01 (sept, 1H, J = 6.9 Hz), 3.77 (s, 3H), 3.00 (t, 4H, J = 6.1 Hz), 1.84 (t, 4H, J = 6.3 Hz), 1.15

(d, 6H, $J = 6.5$ Hz). ^{13}C NMR (DMSO-d_6): 160.4, 159.0, 138.8, 121.0, 120.1, 106.0, 52.8, 51.4, 40.3, 24.2, 22.5. HRMS: calcd for [M + H$^+$] $C_{14}H_{22}N_3O_3$, 280.1656; found, 280.1656. R_t: 6.21, method F.

Methyl-2-benzylcarbamoyl-3-diallylamino-1*H*-pyrrole-5-carboxylate (14Da). Yield: 51%. Isolated as an orange gum. ^{1}H NMR (DMSO-d_6): δ 11.90 (s, 1H), 9.24 (t, 1H, $J = 5.4$ Hz), 7.27−7.37 (m, 5H), 6.85 (s, 1H), 5.67−5.76 (m, 2H), 5.01−5.11 (m, 4H), 4.50 (d, 2H, $J = 5.7$ Hz), 3.75 (s, 3H), 3.46 (d, 4H, $J = 6.2$ Hz). ^{13}C NMR (DMSO-d_6): δ 160.3, 159.6, 139.2, 137.6, 134.6, 128.4, 127.3, 127.0, 124.0, 122.1, 118.2, 110.6, 58.3, 51.4, 41.9. HRMS: calcd for [M + H$^+$] $C_{20}H_{24}N_3O_3$, 354.1812; found, 354.1808. R_t: 23.08, method A; 14.98, method C; 6.36, method E.

Methyl-2-methoxyethylcarbamoyl-3-diallylamino-1*H*-pyrrole-5-carboxylate (14Db). Yield: 51%. Isolated as an orange gum. ^{1}H NMR (DMSO-d_6): δ 12.15−11.75 (br s, 1H), 9.04 (s, 1H), 6.92 (s, 1H), 5.83−5.75 (m, 2H), 5.10−5.17 (m, 4H), 3.76 (s, 3H), 3.57 (br s, 4H), 3.45 (s, 4H), 3.29 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 160.3, 159.6, 137.4, 134.7, 124.3, 122.1, 118.2, 110.7, 70.8, 58.4, 58.0, 51.5, 37.9. HRMS: calcd for [M + H$^+$] $C_{16}H_{24}N_3O_4$, 322.1761; found, 322.1766. R_t: 22.00, method A; 12.25, method C; 5.12, method E.

Methyl-2-isopropylcarbamoyl-3-diallylamino-1*H*-pyrrole-5-carboxylate (14Dc). Yield: 56%. Isolated as a yellow gum. ^{1}H NMR (DMSO-d_6): δ 11.75 (s, 1H), 8.78 (d, 1H, $J = 7.7$ Hz), 6.85 (s, 1H), 5.80−5.72 (m, 2H), 5.16−5.08 (m, 4H), 4.03 (sept, 1H, $J = 6.8$ Hz), 3.75 (s, 3H), 3.50 (d, 4H, $J = 6.2$ Hz), 1.16 (d, 6H, $J = 6.5$ Hz). ^{13}C NMR (DMSO-d_6): δ 160.3, 158.7, 137.3, 134.5, 124.2, 121.8, 118.2, 110.5, 58.2, 51.4, 40.1, 22.7. HRMS: calcd for [M + H$^+$] $C_{16}H_{24}N_3O_3$, 306.1812; found, 306.1819. R_t: 13.00, method C; 5.44, method E.

2-[(*S*)-1′-Hydroxycarbonyl-3′-methylbutyl]carbamoyl-3-morpholino-1*H*-pyrrole-5-carboxylic Acid (15). Yield: 65%. Light beige powder. $[\alpha]_D^{23}$ 16.0° (c 1.7, DMSO). mp: 92 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 11.75 (s, 1H), 9.06 (d, 1H, $J = 8.0$ Hz), 6.81 (s, 1H), 4.50 (m, 1H), 3.73 (m, 4H), 2.86 (m, 4H), 1.64 (m, 3H), 0.92 (d, 3H, $J = 9.2$ Hz), 0.91 (d, 3H, $J = 9.1$ Hz). ^{13}C NMR (DMSO-d_6): δ 174.1, 161.3, 159.3, 140.6, 123.7, 121.0, 108.1, 66.5, 53.7, 50.0, 41.0, 24.6, 22.8, 21.8. HRMS: calcd for [M + H$^+$] $C_{16}H_{23}N_3O_6$, 354.1660; found, 354.1654. R_t: 9.80, method C.

2,4-Di(methoxyethylcarbamoyl)-3-(dimethylamino)-1*H*-pyrrole-5-carboxylic Acid (17): Traces. ^{1}H NMR (DMSO-d_6): δ 12.51 (s, 1H), 11.34 (s, 1H), 8.72 (s, 1H), 3.52 (s, 8H), 3.32 (s, 6H), 2.74 (s, 6H). FAB-MS: *m*/*z* 357.1 [M+H]$^+$. R_t: 11.51, method D.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectral data for **5**, **7**−**9**, **11**, **13**−**15**, and **17** and representative LCMS traces for compounds **13B**, **14B**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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