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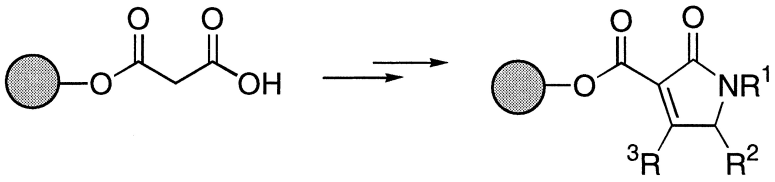

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A Novel Solid-Phase Synthesis of Carboxypyrrolinones

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A solid-phase organic synthesis method has been developed for the preparation of 3-carboxypyrrolinones **9**. Treatment of polymer-bound malonic acid with amino alcohols afforded the malonamide resin products **6**. Benzyl and alkyl amino alcohols were prepared in solution via a two-step procedure without purification and were coupled to the resin directly using a resin capture strategy. Polymer loadings and product conversions were determined by direct cleavage of resin-bound materials and analysis by ^{1}H NMR spectroscopy with an internal standard. Treatment of the polymer-bound malonamides with TFA released the malonamic acids, **10**, which underwent further reaction to afford the trifluoroacetate derivatives **11**. Secondary amides underwent an additional cyclization to afford oxazoles **12**. The malonamide resins **6** can be oxidized to the corresponding ketones **7** by treatment with CrO_2(O-*t*-Bu)$_2$, which can in turn be cyclized in the presence of LDA or LHMDS to afford the carboxypyrrolinones **8**. TFA treatment releases the free carboxypyrrolinones, **9**, in 43−80% overall yield.

Introduction

Combinatorial methods for the production of compound libraries have recently received much attention as a way to accelerate the chemical discovery process.[1−5] As a result, there is a renewed interest in solid-phase organic synthesis (SPOS), particularly in extending traditional peptide and oligonucleotide synthesis to other organic reactions.[6−8] The chemistry of active methylene compounds, particularly as precursors for heterocycles, has been a fruitful area in pharmaceutical and agrochemical discovery. Although several groups have focused on the preparation of resin-bound intermediates containing active methylenes and their use for the preparation of heterocycles,[9,10] there are still many transformations that have not yet been reported via SPOS.

The pyrrole ring system is an attractive target since it is the central scaffold in a variety of known agrochemicals and pharmaceutical drugs.[11−13] We were particularly interested in 3-carboxypyrrolinones based on the similarity of these structures to known chemical hybridizing agents.[14−18]

Previous solution-phase methods to prepare these types of compounds include intramolecular Aza−Wittig reactions or electroreduction of 4*H*-1,3-thiazines to afford the alkoxy derivatives,[19−21] rhodium(II)-catalyzed reactions of α-diazoamides,[22,23] carbonylation of lithiated butyrolactams,[24] oxidation of the corresponding tetrahydropyrroles,[25,26] and cyclocondensation of appropriately substituted malonamides.[27] These methods often involve lengthy synthetic sequences and use of protecting groups and, in some cases, proceed in low yields. We report here a simple and efficient preparation of 3-carboxypyrrolidones via solid-phase synthetic methods.

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Results and Discussion

3-Carboxypyrrolinones were prepared using a combination of solution-phase and solid-phase techniques, as outlined in Scheme 1.

Wang resin-bound malonic acid, **5**, was prepared by literature methods.[28] Treatment of **5** with an amino alcohol in the presence of HOBt/DIC affords the corresponding products, **6a**−**k**, in excellent yields and with complete chemoselectivity (Table 1). High coupling yields were also obtained with less reactive N-aryl amino alcohols, although electron-neutral or -deficient aromatic systems afforded slightly lower yields than the corresponding electron-rich systems.

Commercially unavailable alkyl and benzyl amino alcohols (**4b, 4c, 4i**−**k)** were prepared by a two-step reductive amination procedure in solution as outlined in Scheme 1. No workup or purification was required. An excess of the aldehyde or ketone was used to ensure that no primary amino alcohol remained, since it would compete with the desired product in the coupling reaction. The amino alcohol, **4**, was then selectively coupled to the resin-bound malonic acid using a resin capture strategy, since the amino group of **4** is more reactive than the alcohol byproduct resulting from reduction of excess aldehyde or ketone. Even with a large excess of the crude reaction mixture, products resulting from coupling of the alcohol byproduct were not observed. Commercially unavailable aryl amino alcohols (**4e**−**h)** were prepared by addition of analines to the corresponding epoxide, which was in turn prepared from the appropriate alkene as outlined in the Experimental Section.

The effect of amino alcohol stoichiometry on coupling yield was next explored, and the results are shown in Table 1. Excess amino alcohol is required to achieve high coupling yields. Optimal yields were obtained with 4 equiv of amino alcohol.

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Scheme 1

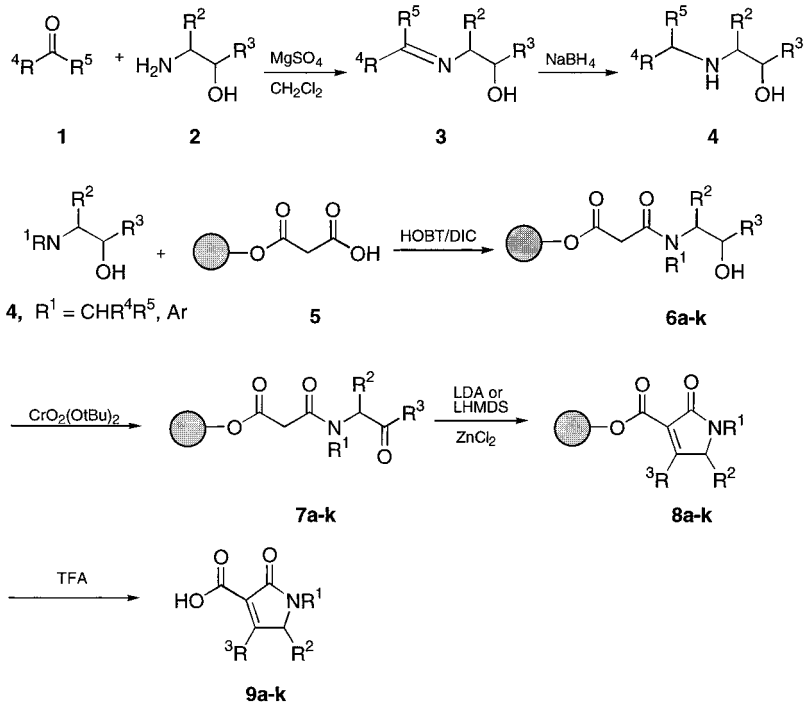


Table 1. Reactions of Amino Alcohol with Malonic Acid Resin, **5**, To Afford Resins, **6**[a,b]

entry	R^1	R^2	R^3	theoretical loading[c] (mequiv/g)	loading (mequiv/g)	equiv of **4**	yield of **10**−**12** (%)
a	H	H	Ph	0.79	0.76	5.0	96
				0.80	0.76	4.0	95
				0.82	0.72[d]	2.0	88
				0.82	0.65[d]	1.5	79
				0.83	0.53[d]	1.0	64
b	CH_2Ph	H	Ph	0.77	0.74	4.0	96
c	CH_2(4-OMePh)	H	Ph	0.76	0.75	4.0	99
d	Ph	H	H	0.82	0.67	2.0	82
e	4-ClPh	H	Et	0.81	0.59	2.0 (×2)[b]	73
f	4-ClPh	H	*i*-Bu	0.79	0.63	2.0 (×2)[b]	80
g	4-OMePh	H	Et	0.82	0.81	2.0 (×2)[b]	99
h	3,5-diMePh	H	Et	0.64	0.57	2.0 (×2)[b]	89
i	*i*-Pr	H	Ph	0.84	0.87	4.0	103
j	$CH_2CH(Et)_2$	Me	Ph	0.81	0.62	4.0	77
k	$CH_2CH(Et)_2$	Ph	Ph	0.77	0.55	4.0	71

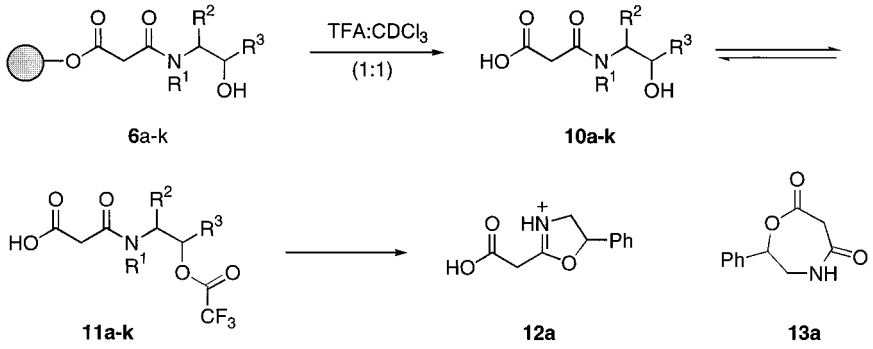
[a] All conversions of **5** to **6a**−**k** were greater than 95% as determined by ^{1}H NMR spectroscopy except when noted. The loading of the resins, **6a**−**k**, were determined by ^{1}H NMR spectroscopy.[29] [b] Two sequential treatments were employed, each using 2 equiv of amino alcohol. [c] Based on loading of the malonic-acid-bound resin starting material. [d] Decreased loading and yield reflect incomplete conversion to product.

The product yields were determined by treatment of the resin with TFA:$CDCl_3$ (1:1) and analysis of the cleavage products by ^{1}H NMR spectroscopy using hexamethyldisiloxane (HMDS) as an internal standard.[29] This method allowed the product identity, purity, and resin loading to be assessed accurately. As discussed below, the spectroscopic analysis was also extremely useful in elucidating subsequent reactions of the products after cleavage.

The products **10a**−**k**, once cleaved from the resin, are not stable to the cleavage conditions and undergo further reaction over time to afford a mixture of products (Scheme 2). When resin **6a** was treated with TFA:$CDCl_3$ (1:1), **10a** was initially observed, followed by the appearance of the trifluoroacetate **11a** and finally the cyclized product assigned structure **12a**. (Scheme 2). For resins **6b**−**k**, two products were observed upon cleavage. On the basis of comparison of the spectra to those for **10a**−**12a**, these two products were assigned structures **10b**−**k** and **11b**−**k**. Whereas one amide conformer was observed for **10a** and **11a**, the N-substituted compounds **10b**−**k** and **11b**−**k** generally existed as two amide conformers.

To confirm these results and structure assignments, compound **10a** was prepared independently and, when subjected to the cleavage solvents and conditions, afforded **11a** and **12a** in a ratio identical to that observed during the cleavage of resin **6a**, as judged by ^{1}H and ^{13}C NMR spectroscopy. The time-dependent disappearance of **10a** and formation of **11a** and **12a** in this experiment are shown in Figure 1.

Scheme 2



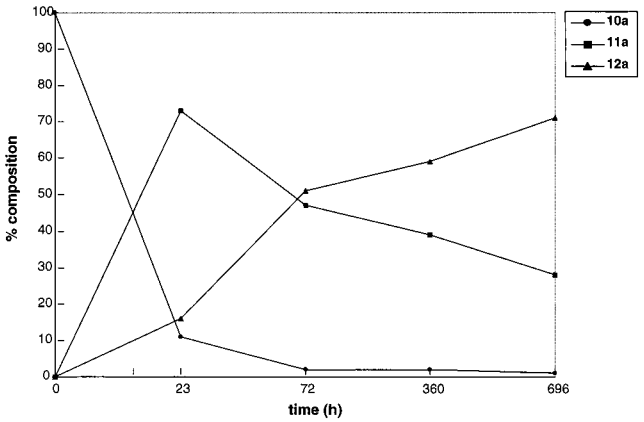


Figure 1. Time-dependent disappearance of **10a** and formation of **11a** and **12a**.

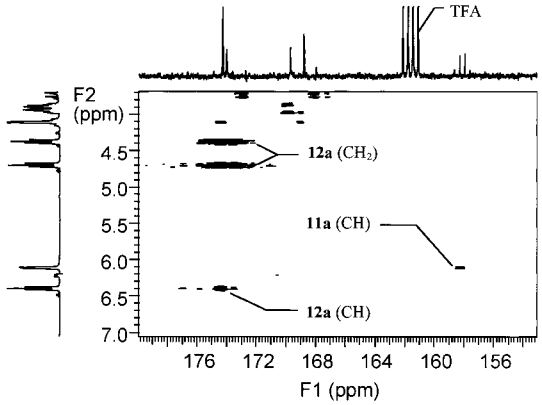


Figure 2. HMBC spectrum of compounds **11a** and **12a** (≅1:1).

Oxazepine, **13a**, which is known to form under similar conditions,[30] was ruled out as the cyclized product by a heteronuclear multiple bond coherence (HMBC) experiment which detects couplings between protons and carbons (Figure 2). The HMBC experiment was performed after dissolving **10a**, generated independently, in TFA:$CDCl_3$ and allowing the solution to stand at room temperature for 48−72 h before acquiring the spectral data. During this time frame, **10a** had been consumed, and the ratio of **11a:12a** was approximately 1:1. For **13a**, the methine proton resonance and the methylene proton resonances α to nitrogen should be three-bond coupled to different carbonyls, whereas for **12a** they should be three-bond coupled to only one carbonyl-type resonance. The HMBC experiment also confirmed the structural assignment for **11a** since the three-bond coupling of the methine proton to the carbonyl of the $COCF_3$ group was observed.

Table 2. $CrO_2(O\text{-}t\text{-}Bu)_2$ Oxidation of Resins **6** To Afford Resins **7**[a]

entry	R^1	R^2	R^3	loading (mequiv/g)	yield[b] of **14** (%)
a	H	H	Ph	0.56	75
b	CH_2Ph	H	Ph	0.64	86
c	CH_2(4-OMePh)	H	Ph	0.64	84
d	Ph	H	H		0
e	4-ClPh	H	Et	0.55	93
f	4-ClPh	H	*i*-Bu	0.42	67
g	4-OMePh	H	Et	0.53	65
h	3,5-diMePh	H	Et	0.45	88
i	*i*-Pr	H	Ph	0.69	79
j	$CH_2CH(Et)_2$	Me	Ph	0.38	61
k	$CH_2CH(Et)_2$	Ph	Ph	0.55	95

[a] All conversions of **6** to **7** were greater than 95% as determined by ^{1}H NMR spectroscopy. The loading of the resins, **7a**−**k**, was determined by ^{1}H NMR spectroscopy.[29] [b] Yields are based on the theoretical loading of **7**.

Several oxidizing reagents were explored for the conversion of **6** to **7**. The Swern reagent is reported to be an effective oxidant for resin-bound substrates,[31−33] but in our hands, significant amounts of unreacted starting material were recovered in addition to the desired product. Additionally, the Swern reagent is unstable at temperatures above 10 °C. A second Moffatt-type reagent, SO_3/pyridine, is also reported for SPOS oxidations and is stable at room temperature.[34] This reagent was effective for many, but not all, substituents. In particular, N-aryl substituted compounds were not completely oxidized under these conditions. In those examples where the oxidation was successful, two amide conformers were observed after cleavage. The most broadly applicable oxidizing reagent, in our hands, was $CrO_2(O\text{-}t\text{-}Bu)_2$, which was generated in situ according to the procedure of Leznoff et al.[35] With this reagent, generally, one amide conformer was observed upon cleavage of the product from the resin. There was some broadening observed in the ^{1}H NMR spectra, presumably due to trace amounts of residual chromium salts.

The oxidation proceeded smoothly for most substrates to afford the product resins **7a**−**k** in good yields (Table 2). These resins were cleaved in TFA:$CDCl_3$ to afford the product ketones, **14** (Scheme 3). We were, however, unable to oxidize primary alcohols to the corresponding aldehydes (entry **7d**). The starting alcohol was consumed in the reaction but no product was observed.

Cyclization of the oxidized products, **7**, was accomplished with strong hindered bases such as lithium diisopropylamide (LDA) or lithium hexamethyldisilazane (LHMDS) in the

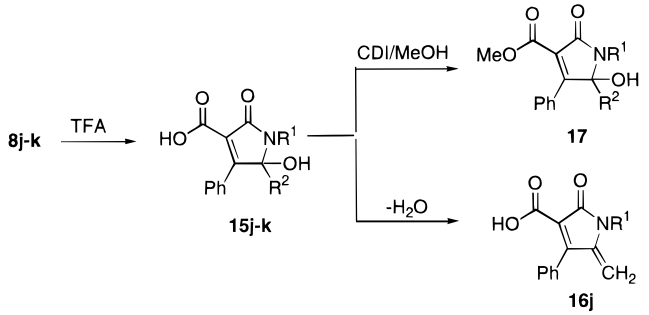
Scheme 3

Table 3. Cyclization of Resins **7** to **8**[a]

entry	R^1	R^2	R^3	loading (mequiv/g)	yield[b] of **9** (%)
a	H	H	Ph		0
b	CH_2Ph	H	Ph	0.53	93
c	CH_2(4-OMePh)	H	Ph	0.61	94
e	4-ClPh	H	Et	0.45	82
g	4-OMePh	H	Et	0.40	85
h	3,5-diMePh	H	Et	0.41	90
i	*i*-Pr	H	Ph	0.48	69

[a] All conversions of **7** to **8** were greater than 95% as determined by ^{1}H NMR spectroscopy. The loading of the resins, **8a**−**k**, was determined by ^{1}H NMR spectroscopy.[29] [b] Yields are based on the theoretical loading of **8**.

Scheme 4



presence of Lewis acids to afford the resin-bound products, **8** (Table 3). Cleavage from the resin afforded the carboxypyrrolinones **9**. We were unable to cyclize the NH compound **7a** under any conditions. Compound **7f** underwent cyclization but did not afford a clean product. ^{1}H and ^{13}C NMR spectra suggest that the carboxypyrrolinones exist as keto tautomers. The cyclized products, once cleaved from the resin, undergo decarboxylation upon continued exposure to TFA. Even after removal of TFA, the products decompose over time as has been noted previously.[26,36] The resin-bound products, **8**, although more stable than the cleaved products, did decompose upon storage at room temperature over months or upon heating to 50 °C for several hours.

Two pyrrolinones prepared by cyclization using this method, **8j**−**k**, underwent further reactions to give products not observed in examples where R^2 = H. When R^2 = phenyl (**8k**), two cleavage products were noted by HRMS and ^{13}C NMR spectroscopy, one being the expected product, **9k**. The second product gave a HRMS consistent with the addition of oxygen. This compound, unlike the expected product, was stable to decarboxylation, consistent with possessing a fully substituted pyrrolinone ring. The crude product was isolated free of TFA and treated with carbonyldiimidazole, followed by methanol. After purification, methyl ester **17** was isolated, which supports the cyclic carbinol structure **15k** as the original coproduct (Scheme 4). This product presumably arises from autoxidation of the anionic species during cyclization.

Table 4. Comparison of Overall Isolated Yields with NMR Calculated Yields[a]

entry	R^1	R^2	R^3	NMR yield (%)	isolated yield (%)
9e	4-ClPh	H	Et	55	53
14b	CH_2Ph	H	Ph	75	63
14c	CH_2(4-OMePh)	H	Ph	73	69

[a] Overall yields are based on the loading of the starting malonic-acid-bound resin (**5**).

When R^2 = methyl (**8j**), HRMS of the product after cleavage with TFA gave a result consistent with the expected decarboxylated product with an additional loss of two mass units. NMR spectra support the structure **16j**, which presumably results from autoxidation to **15j**, followed by loss of water.

Finally, selected intermediates and products were isolated, and the overall isolated yield was compared to the yield calculated by NMR spectroscopic integration of product peaks vs an internal standard (Table 4). We consistently obtained yields that correlated well with the calculated NMR yields. These results support that the NMR spectroscopic method for calculating resin loading and product yields is accurate.[37]

In summary, we have demonstrated a simple and efficient synthesis of carboxypyrrolinones via solid-phase techniques. We have also shown the broad scope of the addition of amino alcohols to resin-bound malonic acid and have characterized the subsequent reactions of these products upon cleavage from the resin with TFA. Finally, we have examined various reagents for the oxidation and cyclization steps and have explored the scope of these reactions. On the basis of our results, these useful reactions are likely to find broad application for the preparation of combinatorial libraries.

Experimental Section

General Procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 equipped with a Nalorac 5 mm four-nucleus probe (400 MHz ^{1}H, 100 MHz ^{13}C). The HMBC spectrum was recorded on a Varian Inova 500 (500 MHz ^{1}H, 125 MHz ^{13}C) spectrometer using a 5 mm Nalorac gradient quad nucleus inverse detection probe. The HMBC data set consisted of 128 increments of a hypercomplex data set using 168 scans per increment and a double quantum evolution time of 100 ms. Polymer-supported reactions were carried out using flasks fitted with a glass frit at the bottom and a sidearm connected to a needle valve (Aldrich, Z28,330-4). Prior to carrying out reactions, the polymer-bound starting material was allowed to swell in the reaction solvent for 10−20 min under an inert atmosphere. Wang or *p*-alkoxybenzyl alcohol resin[38] was obtained from Advanced ChemTech (Louisville, KY) and Chem-Impex International (Wood Dale, IL). To determine resin loading, an aliquot of resin (50−100 mg) was weighed into a fritted syringe barrel and cleaved with a TFA:$CDCl_3$ solution (1:1, 1.0 mL/100 mg resin) containing hexamethyldisiloxane (HMDS, 9−11 mmol/mL) as an internal standard. The resin loading was determined by ^{1}H NMR spectroscopy by integrating characteristic and resolved protons in the products vs the CH_3 protons in HMDS.[29]

General Procedure for the Preparation of Amino Alcohols 4b, 4c, 4i−k. The primary amino alcohol (0.5−40 mmol, 1 equiv) was dissolved in CH_2Cl_2 (1−30 mL) in a round-bottomed flask or in a 4 dram vial (for library preparation). To the solution was added the aldehyde (1.05−1.1 equiv) and $MgSO_4$ (0.1−4 g), and the resulting mixture was agitated at room temperature for 8−18 h. The mixture was filtered, and the filtrate concentrated under a stream of nitrogen. The resulting residue was dissolved in MeOH (3−50 mL) and cooled in an ice bath, and $NaBH_4$ (1.5 equiv) was added. The reaction was warmed to room temperature and agitated for 8−18 h then quenched with water (2.5−150 mL) and HCl (10% aqueous, 0.5−50 mL). The mixture was concentrated under a stream of nitrogen, and the residue was dissolved in ethyl acetate (2.5−150 mL) and washed with water (3 × 3−100 mL). The ethyl acetate solution was dried over $MgSO_4$ and concentrated under a stream of nitrogen. The products were >95% pure based on NMR spectroscopy, and the impurity was generally the alcohol that results from reduction of excess aldehyde.

1-Hydroxy-2-(phenylmethylamino)-1-phenylethane (4b). The reaction was carried out according to the general procedure starting with 2-amino-1-phenylethanol (5.08 g, 37.03 mmol) and benzaldehyde (4.14 g, 39 mmol, 1.05 equiv) to afford the product as a white solid (6.73 g, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.23 (m, 10H), 4.72 (dd, J = 8.9, 3.5 Hz, 1H), 3.81 (dd, J = 19.2, 13.2 Hz, 2H), 2.91 (dd, J = 12.1, 3.5 Hz, 1H), 2.74 (dd, J = 12.1, 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 139.9, 128.5, 128.3, 128.1, 127.5, 127.1, 125.8, 71.8, 56.5, 53.5.

1-Hydroxy-2-(4-methoxyphenyl)methylamino-1-phenylethane (4c). The reaction was carried out according to the general procedure starting with 2-amino-1-phenylethanol (5.08 g, 37.03 mmol) and 4-methoxybenzaldehyde (5.30 g, 39 mmol, 1.05 equiv) to afford the product as a white solid (8.47 g, 89%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.24 (m, 5H), 7.20 (d, J = 7.8 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.71 (dd, J = 8.9, 3.5 Hz, 1H), 3.79 (s, 3H), 3.75 (dd, J = 21.3, 14.2 Hz, 2H), 2.90 (dd, J = 12.1, 3.5 Hz, 1H), 2.72 (dd, J = 12.1, 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 142.5, 132.0, 129.4, 129.3, 128.6, 128.3, 127.4, 125.8, 113.9, 113.8, 71.8, 56.4, 55.2, 52.9.

1-Hydroxy-2-(isopropylamino)-1-phenylethane (4i). The reaction was carried out according to the general procedure starting with 2-amino-1-phenylethanol (1.1 g, 8.0 mmol) and acetone (5 mL, 68 mmol) to afford the product as a white solid (1.2 g, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.26 (m, 5H), 4.66 (dd, J = 8.8, 3.2 Hz, 1H), 2.92 (dd, J = 12.0, 3.2 Hz, 1H), 2.86−2.78 (m, 1H), 2.64 (dd, J = 12.4, 8.8 Hz, 1H), 1.07 (d, J = 6.4 Hz, 3H), 1.05 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 128.5, 127.6, 125.9, 72.1, 54.7, 48.9, 23.3, 23.1.

(1*R*,2*S*)-2-(2-Ethylbutylamino)-1-hydroxy-1-phenylpropane (4j). The reaction was carried out according to the general procedure starting with (1*R*,2*S*)-2-amino-1-hydroxy-1-phenylpropane (0.92 g, 6.1 mmol) and 2-ethylbutyraldehyde (790 μL, 6.4 mmol) to afford the product as a white solid (1.42 g, 100%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.18 (m, 5H), 4.73 (d, J = 3.7 Hz, 1H), 2.90−2.82 (m, 1H), 2.54 (dd, 11.2, 5.0 Hz, 1H), 1.60 (m, 1H), 1.38−1.27 (m, 4H), 0.86 (t, J = 7.0 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H), 0.78 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 128.0, 126.9, 126.0, 72.7, 58.7, 49.8, 41.2, 24.0, 24.0, 14.7, 11.0, 10.9.

1-Hydroxy-1,2-diphenyl-2-(2-ethylbutylamino)ethane (4k). The reaction was carried out according to the general procedure starting with 2-amino-1,2-diphenylethanol (1.30 g, 6.1 mmol) and 2-ethylbutyraldehyde (790 μL, 6.4 mmol) to afford the product as a white solid (1.8 g, 100%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.03 (m, 10H), 4.80 (d, J = 5.3 Hz, 1H), 3.82 (d, J = 5.6 Hz, 1H), 2.40 (dd, J = 11.8, 4.4 Hz, 1H), 2.36 (dd, J = 11.8, 4.2 Hz, 1H), 1.25−1.18 (m, 4H), 0.89 (m, 1H), 0.78−0.70 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 139.4, 128.1, 128.0, 127.8, 127.4, 126.6, 76.2, 69.1, 49.9, 41.0, 24.0, 23.9, 14.7, 10.9, 10.8.

General Procedure for Preparation of Amino Alcohols 4e−h. The required epoxides were prepared by treatment of the corresponding alkenes with *m*-chloroperbenzoic acid.[39] Each epoxide (0.10 mol) was combined with the corresponding aniline (0.10 mol) and cobalt(II) chloride (0.023 mol) in anhydrous CH_3CN (100 mL) and heated for 24 h at 45 °C.[40] Workup and purification by recrystallization or flash chromatography (CH_2Cl_2:hexanes, 3:1) afforded the desired amino alcohol.

1-(4-Chlorophenylamino)-2-hydroxybutane (4e). Treatment of 1,2-epoxybutane (5.8 g, 0.08 mol) with 4-chloroaniline (10.2 g, 0.08 mol) afforded the product after purification as a white solid (3.5 g, 22%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 8.6 Hz, 2H), 6.59 (d, J = 8.6 Hz, 2H), 3.72−3.81 (m, 1H), 3.24 (dd, J = 12.6, 3.2 Hz, 1H), 2.99 (dd, J = 12.6, 8.5 Hz, 1H), 1.64−1.50 (m, 2H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 129.2, 122.5, 114.5, 71.7, 50.0, 28.1, 10.0.

1-(4-Chlorophenylamino)-2-hydroxy-4-methylpentane (4f). Treatment of 1,2-epoxy-4-methylpentane (3.9 g, 0.04 mol) with 4-chloroaniline (5.0 g, 0.04 mol) afforded the product after purification as a brown solid (2.6 g, 29%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 8.7 Hz, 2H), 6.60 (d, J = 8.7 Hz, 2H), 3.99−3.90 (m, 1H), 3.25 (dd, J = 12.6, 3.2 Hz, 1H), 2.99 (dd, J = 12.6, 8.4 Hz, 1H), 1.91−1.79 (m, 1H), 1.57−1.47 (m, 1H), 1.39−1.28 (m, 1H), 1.01 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 129.2, 122.4, 114.4, 68.6, 50.8, 44.3, 24.7, 23.5, 22.2.

2-Hydroxy-1-(4-methoxyphenylamino)-butane (4g). Treatment of 1,2-epoxybutane (4.6 g, 0.07 mol) with *p*-anisidine (8.0 g, 0.07 mol) afforded the product after purification as a white solid (4.8 g, 37%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, J = 8.9 Hz, 2H), 6.75 (d, J = 8.9 Hz, 2H), 3.82 (m, 1H), 3.79 (s, 3H), 3.27 (dd, J = 12.6, 3.1 Hz, 1H), 3.02 (dd, J = 12.6, 8.9 Hz, 1H), 1.65−1.54 (m, 2H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 141.1, 115.8, 115.0, 71.4, 55.9, 52.0, 28.0, 10.0.

1-(3,5-Dimethylphenylamino)-2-hydroxybutane (4h). Treatment of 1,2-epoxybutane (4.7 g, 0.07 mol) with 3,5-dimethylaniline (8.0 g, 0.07 mol) afforded the product after purification as a white solid (4.4 g, 35%): ^{1}H NMR (300

MHz, $CDCl_3$) δ 6.52 (s, 1H), 6.46 (s, 2H), 3.85−3.82 (m, 1H), 3.31 (dd, J = 12.8, 3.0 Hz, 1H), 3.06 (dd, J = 12.8, 8.9 Hz, 1H), 2.29 (s, 6H) 1.62−1.54 (m, 2H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 139.3, 121.6, 112.7, 71.3, 51.5, 28.0, 21.5, 10.0.

General Procedure for Coupling Amino Alcohols to Wang Resin-Bound Malonic Acid. A solid-phase synthesis (SPS) flask was charged with Wang resin-bound malonic acid, **5**[28] (approximately 2.5 mmol, 1.0 equiv). The resin was washed with anhydrous DMF (2 × 10 mL) and then suspended in DMF (10 mL) with stirring. HOBT (10 mmol, 4 equiv) was dissolved in DMF (3 mL) and added to the resin via syringe. The amino alcohol (10 mmol, 4 equiv) was dissolved in DMF (3 mL) and transferred to the resin mixture via syringe. DIC (10 mmol, 4 equiv) was added to the reaction neat via syringe, and the mixture was stirred at room temperature for 12−120 h. The resin was filtered and washed consecutively with CH_2Cl_2 (3 × 15 mL), MeOH (4 × 15 mL), and CH_2Cl_2 (5 × 15 mL) and then filtered and dried under vacuum to afford a yellow resin. The loading was calculated by ^{1}H NMR spectroscopy as described in the general procedures. The product malamido alcohols are not stable to the cleavage conditions and undergo further reaction over time to afford a mixture of products. For the initially formed NH malamido alcohols, one amide conformer is observed, while for the N-substituted compounds, generally two amide conformers are observed initially. For these reasons, the NMR spectra for the cleaved products are very complicated and, except for the NH example, were not analyzed in detail. The assignment is based on HRMS data and the characterization of the oxidation product from the next step.

Preparation and Cleavage of Resin 6a. The reaction was carried out using 2.76 mmol of starting material resin **(5)** to afford **(6a)** as a yellow resin product (3.30 g, 98% by wt). An aliquot (92.2 mg) was cleaved, and the loading was calculated using the methine proton (0.73 mmol/g, 89% of theoretical) and the phenyl protons (0.81 mmol/g, 98% of theoretical) in the products. Three products **(10a−12a)** were observed in a ratio of 8.7:5.4:1.0.

3-(2-Hydroxy-2-phenylethylamino)-3-oxo-propionic Acid (10a): Yield 59.5%; ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 8.02 (bs, 1H), 7.45−7.36 (m, 5H), 5.11 (dd, J = 8.4, 3.6 Hz, 1H), 3.87 (ddd, J = 14.4, 6.2, 3.3 Hz, 1H), 3.75 (ddd, J = 14.4, 8.5, 5.8 Hz, 1H), 3.65 (s, 2H); HRMS calcd for (M + H) ($C_{11}H_{14}NO_4$) 224.0923, found 224.0939.

3-(2-Phenyl-2-trifluoroacetyloxyethylamino)-3-oxo-propionic Acid (11a): Yield 31.9%; ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.82 (bs, 1H), 7.57−7.37 (m, 5H), 6.09 (dd, J = 8.4, 4.0 Hz, 1H), 3.98 (ddd, J = 14.7, 6.3, 4.2 Hz, 1H), 3.88 (ddd, J = 14.7, 8.5, 6.1 Hz, 1H), 3.62 (s, 2H).

4,5-Dihydro-5-phenyl-2-oxazolacetic Acid (12a): Yield 6.6%; ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.87 (bs, 1H), 7.57−7.37 (m, 5H), 6.34 (t, J = 1.0 Hz, 1H), 4.71 (dd, J = 12.6, 10.7 Hz, 1H), 4.38 (dd, J = 12.6, 9.4 Hz, 1H), 4.15 (d, J = 19.3 Hz, 1H) 4.09 (d, J = 19.6 Hz, 1H).

Preparation and Cleavage of Resin 6b. The reaction was carried out using 2.69 mmol of starting material resin **(5)** to afford **(6b)** as a yellow resin (3.57 g, 102% by wt). An aliquot (101.6 mg) was cleaved, and the loading was calculated using the phenyl protons in the products (0.74 mmol/g, 96% of theoretical): HRMS calcd for (M + H) ($C_{18}H_{20}NO_4$) 314.1392, found 314.1410.

Preparation and Cleavage of Resin 6c. The reaction was carried out using 2.79 mmol of starting material resin **5** to afford **6c** as a yellow resin (3.66 g, 101% by wt). An aliquot (107.3 mg) was cleaved, and the loading was calculated using the phenyl protons in the products (0.75 mmol/g, 99% of theoretical): HRMS calcd for (M + H) ($C_{19}H_{22}NO_5$) 344.1498, found 344.1504.

Preparation and Cleavage of Resin 6d. The reaction was carried out with Wang malonate resin **(5)** (2.8 g, 2.5 mmol), amino alcohol **(4d)** (5.0 mmol), HOBt (5.0 mmol), and DIC (5.0 mmol). The resin was washed, dried, and treated again with amine under the same conditions to afford **6d** as a yellow resin (2.9 g, 93% by wt). An aliquot of resin (62.3 mg) was cleaved, and loading was determined by direct cleavage (0.67 mmol/g, 82% of theoretical). Two products were observed in a ratio of 56:44.

3-[(2-Hydroxyethyl)(phenyl)amino]-3-oxo-propionic Acid (10d): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.55−7.53 (m, 3H), 7.31−7.29 (m, 2H), 4.09 (t, J = 5.2 Hz, 2H), 4.00 (t, J = 4.8 Hz, 2H), 3.43 (s, 2H).

3-[(Phenyl)(2-trifluoroacetyloxyethyl)amino]-3-oxo-propionic Acid (11d): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.55−7.53 (m, 3H), 7.31−7.29 (m, 2H), 4.60 (t, J = 5.2 Hz, 2H), 4.20 (t, J = 4.8 Hz, 2H), 3.42 (s, 2H); HRMS: calcd for (M + H − CO_2) ($C_{11}H_{13}NO_4$) 180.1025, found 180.1051.

Preparation and Cleavage of Resin 6e. The reaction was carried out with Wang malonate resin **(5)** (0.53 g, 0.5 mmol), amino alcohol **(4e)** (1.0 mmol), HOBt (1.0 mmol), and DIC (1.0 mmol). The resin was washed, dried, and treated again with amine under the same conditions to afford **6e** as a yellow resin (0.50 g, 80% by wt). An aliquot of resin (44.4 mg) was cleaved, and loading was determined by direct cleavage (0.59 mmol/g, 73% of theoretical). Products **10e: 11e** were observed in a ratio of 77:23 1 h after cleavage. Complete conversion to **11e** was observed after 24 h. Upon removal of TFA solvent, **11e** was converted to **10e**.

3-[(4-Chlorophenyl)(2-hydroxybutyl)amino]-3-oxo-propionic Acid (10e): ^{1}H NMR (300 MHz, 1:1 TFA:$CDCl_3$) δ 7.52 (d, J = 8.7 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 4.31 (dd, J = 14.4, 9.6 Hz, 1H), 3.99 (m, 1H), 3.54 (dd, J = 14.4, 2.4 Hz, 1H), 3.44 (s, 2H), 1.60 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); HRMS calcd for (M + H) ($C_{13}H_{16}ClNO_4$) 286.0846, found 286.0872.

3-[(4-Chlorophenyl)(2-trifluoroacetyloxybutyl)amino]-3-oxo-propionic Acid (11e): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.51 (d, J = 9.2 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 5.32 (m, 1H), 4.28 (dd, J = 14.8, 8.8 Hz, 1H), 3.86 (dd, J = 14.8, 2.0 Hz, 1H), 3.40 (s, 2H), 1.76 (m, 2H), 0.96 (t, J = 7.6 Hz, 3H).

Preparation and Cleavage of Resin 6f. The reaction was carried out with Wang malonate resin **(5)** (0.53 g, 0.5 mmol), amino alcohol **(4f)** (1.0 mmol), HOBt (1.0 mmol), and DIC (1.0 mmol). The resin was washed, dried, and treated again with amine under the same conditions to afford **6f** as a yellow

resin (0.52 g, 82% by wt). An aliquot of resin (60.3 mg) was cleaved, and loading was determined by direct cleavage (0.63 mmol/g, 80% of theoretical). Products **10f:11f** were observed in a ratio of 32:68 16 h after cleavage. Upon removal of the TFA solvent, **11f** was converted back to **10f**.

3-[(4-Chlorophenyl)(2-hydroxy-4-methylpentyl)amino]-3-oxo-propionic Acid (10f): ^{1}H NMR (300 MHz, 1:1 TFA:$CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 4.28 (dd, J = 14.4, 8.8 Hz, 1H), 4.14 (m, 1H), 3.54 (dd, J = 14.4, 5.6 Hz, 1H), 3.45 (s, 2H), 1.66−1.52 (m, 2H), 1.00−0.97 (m, 1H), 0.89 and 0.86 (2d, J = 6.4 Hz, 6H); HRMS calcd for (M + H) ($C_{15}H_{20}ClNO_4$) 314.1159, found 314.1177.

3-[(4-Chlorophenyl)(2-trifluoroacetyloxy-4-methylpentyl)amino]-3-oxo-propionic Acid (11f): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.51 (d, J = 9.2 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 5.45 (m, 1H), 4.28 (dd, J = 14.4, 8.8 Hz, 1H), 3.85 (dd, J = 14.4, 2.0 Hz), 3.41 (s, 2H), 1.75−1.68 (m, 1H), 1.49−1.40 (m, 1H), 1.34−1.24 (m, 1H), 0.93 and 0.90 (2d, J = 6.4 Hz, 6H).

Preparation and Cleavage of Resin (6g). The reaction was carried out with Wang malonate resin **(5)** (0.53 g, 0.5 mmol), amino alcohol **(4 g)** (1.0 mmol), HOBt (1.0 mmol), and DIC (1.0 mmol). The resin was washed, dried, and treated again with amine under the same conditions to afford **6g** as a yellow resin (0.51 g, 83% by wt). An aliquot of resin (58.6 mg) was cleaved, and loading was determined by direct cleavage (0.81 mmol/g, 99% of theoretical). Products **10g:11g** were observed in a ratio of 24:76 16 h after cleavage, and complete conversion to **11g** was observed after 72 h. Upon removal of the TFA solvent, **11g** was converted back to **10g**.

3-[(4-Methoxyphenyl)(2-hydroxybutyl)amino]-3-oxo-propionic Acid (10g): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.23 (d, J = 9.2 Hz, 2H), 7.04 (d, J = 9.2 Hz, 2H), 4.31 (dd, J = 14.8, 8.8 Hz, 1H), 3.90 (s, 3H), 3.51 (dd, J = 14.8, 2.4 Hz, 1H), 3.45 (s, 2H), 1.60 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); HRMS calcd for (M + H) ($C_{14}H_{19}NO_5$) 282.1341, found 282.1356.

3-[(4-Methoxyphenyl)(2-trifluoroacetyloxybutyl)amino]-3-oxo-propionic Acid (11g): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.19 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 9.2 Hz, 2H), 5.30 (m, 1H), 4.30 (dd, J = 14.8, 8.8 Hz, 1H), 3.90 (s, 3H), 3.84 (dd, J = 14.8, 2.4 Hz, 1H), 3.41 (s, 2H), 1.77 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H).

Preparation and Cleavage of Resin 6h. The reaction was carried out with Wang malonate resin **(5)** (0.56 g, 0.5 mmol), amino alcohol **(4h)** (1.0 mmol), HOBt (1.0 mmol), and DIC (1.0 mmol). The resin was washed, dried, and treated again with amine under the same conditions to afford **6h** as a yellow resin (0.50 g, 89% by wt). An aliquot of resin (66.1 mg) was cleaved, and loading was determined by direct cleavage (0.57 mmol/g, 89% of theoretical). Products **10h:11h** were observed in a ratio of 84:16 1 h after cleavage, and complete conversion to **11h** was observed after 72 h. Upon removal of the TFA solvent, **11h** was converted back to **10h**.

3-[(3,5-Dimethylphenyl)(2-hydroxybutyl)amino]-3-oxo-propionic Acid (10h): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.13 (s, 1H), 6.87 (s, 2H), 4.33 (dd, J = 14.4, 9.6 Hz, 1H), 3.99 (m, 1H), 3.51 (dd, J = 14.4, 2.4 Hz, 1H), 3.45 (s, 2H), 2.35 (s, 6H), 1.59 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); HRMS calcd for (M + H) ($C_{15}H_{21}NO_4$) 280.1549, found 280.1550.

3-[(3,5-Dimethylphenyl)(2-trifluoroacetyloxybutyl)amino]-3-oxo-propionic Acid (11h): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.12 (s, 1H), 6.82 (s, 2H), 5.33 (m, 1H), 4.20 (dd, J = 14.4, 8.8 Hz, 1H), 3.94 (dd, J = 14.4, 2.4 Hz, 1H), 3.41 (s, 2H), 2.34 (s, 6H), 1.77 and 1.75 (2q, J = 6.4 Hz, 2H), 0.96 (t, J = 7.2 Hz, 3H).

Preparation and Cleavage of Resin 6i. The reaction was carried out using 0.80 mmol resin to afford a rusty red resin product. An aliquot (103.0 mg) was cleaved. The ^{1}H NMR of the product was very complex and changed with time; however, the loading was calculated using the methyl protons of the isopropyl group (0.87 mmol/g, 103% of theoretical).

3-[(1-Methylethyl)[(2-hydroxy-2-phenyl)ethyl]amino]-3-oxo-propanoic Acid (10i): HRMS calcd for (M + H)-($C_{14}H_{19}NO_4$) 266.1392, found 266.1404.

Preparation and Cleavage of Resin 6j. The reaction was carried out using 1.2 mmol of starting material resin **(5)** and 4.7 mmol of the amino alcohol **(4j)** to afford **(6j)** as a yellow resin product (1.42 g, 98% by wt). An aliquot (99.4 mg) was cleaved, and the loading was calculated using the phenyl protons in the product (0.62 mmol/g, 77% of theoretical). One product was observed and characterized.

3-[(2-Ethylbutyl)[(2-trifluoroacetyloxy-1-methyl-2-phenyl)ethyl]amino]-3-oxo-propanoic Acid (11j): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.50 (m, 3H), 7.31 (m, 2H), 5.72 (d, J = 8.9 Hz, 1H), 4.44 (dq, J = 8.9, 6.6 Hz, 1H), 4.15 (d, J = 17.5 Hz, 1H), 4.08 (d, J = 17.5 Hz, 1H), 3.68 (d, J = 14.1 Hz, 1H), 1.65 (d, J = 6.4 Hz, 3H), 1.51 (m, 1H), 1.31 (m, 4H), 0.93 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H); HRMS calcd for (M + H) ($C_{18}H_{28}NO_4$) 322.2018, found 322.2074.

Preparation and Cleavage of Resin 6k. The reaction was carried out using 1.2 mmol of starting material resin **(5)** and 4.7 mmol of the amino alcohol **(4k)** to afford **(6k)** as a yellow resin product (1.40 g, 91% by wt). An aliquot (110.4 mg) was cleaved, and the loading was calculated using the phenyl protons in the product (0.55 mmol/g, 71% of theoretical). One product was observed and characterized.

3-[(2-Ethylbutyl)(2-trifluoroacetyloxy-1,2-diphenyl)-ethyl]amino]-3-oxo-propanoic Acid (11k): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.50 (m, 6H), 7.36 (m, 2H), 7.26 (m, 2H), 6.09 (d, J = 9.1 Hz, 1H), 5.26 (d, J = 9.0 Hz, 1H), 4.26 (s, 2H), 3.57 (dd, J = 14.4, 9.7 Hz, 1H), 3.32 (dd, J = 14.5, 5.1 Hz, 1H), 1.50 (m, 1H), 1.35 (m, 2H), 1.25 (m, 1H), 1.12 (m, 1H), 0.88 (t, J = 7.4 Hz, 3H), 0.60 (t, J = 7.4 Hz, 3H); HRMS calcd for (M + H − CO_2) ($C_{22}H_{30}NO_2$) 340.2277, found 340.2278.

Solution-Phase Synthesis of (10a): Preparation of Ethyl 3-[(2-Hydroxy-2-phenylethyl)amino]-3-oxo-propanoate. A 500 mL three-necked round-bottomed flask fitted with a nitrogen inlet and magnetic stirring was charged with ethyl malonyl chloride (10.46 g, 69.5 mmol) dissolved in anhydrous CH_2Cl_2 (100 mL). 2-Amino-1-phenylethanol (19.54 g, 142.44 mmol, 2.05 equiv) was dissolved in anhydrous

CH_2Cl_2 (50 mL) and added to the reaction flask dropwise via syringe over 10 min. The reaction was slightly exothermic, and a white precipitate formed. The reaction was stirred for 30 min, and then NH_4Cl aqueous solution (1/2 saturated, 75 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed consecutively with NH_4Cl aqueous solution (1/2 saturated, 2 × 125 mL), H_2O (150 mL), and brine (150 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the product as a orange−yellow oil (96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (bs, 1H), 7.35−7.24 (m, 5H), 4.81 (dd, J = 8.3, 3.5 Hz, 1H), 4.15 (q, J = 7.3 Hz, 2H), 3.90 (bs, 1H), 3.65 (ddd, J = 14.0, 6.7, 3.5 Hz, 1H), 3.33 (ddd, J = 13.7, 8.5, 5.1 Hz, 1H), 3.26 (s, 2H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 166.3, 141.6, 128.3, 127.7, 125.7, 73.0, 61.5, 47.3, 41.2, 13.9.

Preparation of (10a). A 250 mL round-bottomed flask was charged with ethyl 3-(2-hydroxy-2-phenylethyl amino)-3-oxo-propanoate (2.00 g, 8.0 mmol) dissolved in MeOH (8 mL). The reaction was cooled with stirring in an ice bath and NaOH (2.5 N, 9.6 mmol, 1.2 equiv) was added dropwise. The reaction was warmed to room temperature and stirred for 26 h. The methanol was removed in vacuo, and the residue was diluted with water (10 mL) and acidified with concentrated HCl. The aqueous solution was extracted with diethyl ether (4 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford **(10a)** as a pale yellow oil that solidified over time (900 mg, 50%). The product was recrystallized to afford a white crystalline solid (497 mg, 28%): ^{1}H NMR (400 MHz, CD_3CN) δ 7.36−7.26 (m, 5H), 7.22 (bs, 1H), 4.74 (dd, J = 7.8, 4.0 Hz, 1H), 3.50 (ddd, J = 13.6, 6.2, 4.2 Hz, 1H), 3.32 (ddd, J = 13.6, 8.0, 5.6 Hz, 1H), 3.26 (s, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 169.1, 168.4, 142.4, 128.3, 127.5, 126.0, 71.8, 47.0, 38.9. Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.21; H, 5.88; N, 6.27.

Reaction of (10a) in TFA:$CDCl_3$ (1:1) over Time. An NMR tube was charged with **(10a)** (80 mg, 0.36 mmol). The solid was dissolved in $CDCl_3$:TFA (1:1, 700 μL), and ^{1}H and ^{13}C NMR spectra were recorded over time. Proton spectra were identical to those reported above for cleavage of resin **6a**. Carbon spectra are reported below. From t = 48−72 h, an HMBC experiment was collected. At t = 72 h, **10a** was essentially consumed, and the ratio of **(11a:12a)** was approximately 1:1. **(10a):** ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 174.5, 169.9, 138.0, 129.7, 129.5, 126.0, 74.5, 47.2, 39.6. **(11a):** ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 173.9, 168.9, 134.2, 130.1, 129.5, 126.4, 78.9, 44.9, 39.5. **(12a):** ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 174.2, 169.4, 132.8, 132.0, 130.3, 127.2, 90.2, 51.8, 33.0; HRMS calcd for M + H ($C_{11}H_{12}NO_3$) 206.0817, found 206.0804.

Swern Oxidation of 6a To Afford 7a. A 25 mL three-necked round-bottomed flask was charged with CH_2Cl_2 (1 mL) and oxalyl chloride (0.69 mmol, 60 mL, 4.5 equiv) and then cooled in a acetone/CO_2 cold bath for 10 min. DMSO (1.41 mmol, 100 μL, 9.2 equiv) was added via syringe, and the mixture was warmed to −20 °C in a CCl_4/CO_2 cold bath. The Wang resin-bound starting material, **6a** (226.6 mg, 0.15 mmol, 1 equiv), was added all at once, and the heterogeneous reaction was swirled at −20 °C for 4.25 h. NEt_3 (3.1 mmol, 430 μL, 20.1 equiv) was added via syringe, and the reaction was slowly warmed to room temperature. Water (5 mL) was added, and the mixture swirled for 10 min. The reaction mixture was transferred to a solid-phase synthesis flask, drained, and washed consecutively with CH_2Cl_2 (2 × 10 mL), DMF (4 × 10 mL), and CH_2Cl_2 (5 × 10 mL). The resin was then filtered and dried under vacuum to afford **7a** as an amber resin (217.8 mg, 95% by wt). An aliquot of resin (50.4 mg) was weighed into a fritted syringe barrel and cleaved with a TFA:$CDCl_3$ solution (1:1, 0.5 mL) containing hexamethyldisiloxane (HMDS, 10.02 mmol/mL) as an internal standard. The resin loading (0.61 mmol/g, 90% of theoretical) was determined by ^{1}H NMR spectroscopy as described in the general procedures by integrating the methine proton in the cleaved starting material **(10a)** and the CH_2N protons in the cleaved products **(14a)** versus the CH_3 protons in HMDS.[29] Two amide conformers of the product **(14a)** were observed in addition to starting material. The ratio of starting material to each of the conformers was 4.6:4.4:1, and the yield of product was 49%.

3-[(2-oxo-2-phenylethyl)amino]-3-oxo-propionic Acid (14a). Major conformer: 40%; ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 8.40 (bs, 1H), 8.00 (d, J = 7.3 Hz, 2H), 7.74 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.9 Hz, 2H), 4.97 (d, J = 4.7 Hz, 2H), 3.72 (s, 2H). Minor conformer: 9%; ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 8.22 (bs, 1H), 7.95 (d, J = 7.3 Hz, 2H), 7.74 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.9 Hz, 2H), 4.91 (d, J = 5.2 Hz, 2H), 4.52 (s, 2H).

SO_3. Pyridine Oxidation of 6a To Afford 7a. A solid-phase synthesis (SPS) flask was charged with starting material resin, **6a** (217.0 mg, 0.163 mmol, 1.0 equiv). The resin was washed with anhydrous DMSO (2 × 5 mL) and then suspended in DMSO (1 mL) with stirring. NEt_3 (2.52 mmol, 350 μL, 15.4 equiv) was added via syringe and rinsed from the sides of the vessel with DMSO (0.5 mL). Sulfur trioxide/pyridine complex (134.3 mg, 0.84 mmol, 5.2 equiv) was dissolved in DMSO (1 mL) and was added to the reaction via syringe. The sides of the vessel were rinsed with DMSO (0.5 mL), and the reaction was stirred at room temperature for 27 h. The resin was filtered and washed consecutively with DMSO (2 × 10 mL), CH_2Cl_2 (2 × 10 mL), MeOH:H_2O (1:1, 3 × 20 mL), MeOH (3 × 10 mL), and CH_2Cl_2 (6 × 10 mL) and then filtered and dried under vacuum to afford an amber resin (218.5 mg, 99% by wt). The resin loading (0.63 mmol/g, 85% of theoretical) was determined by ^{1}H NMR spectroscopy as described in the general procedures.[29] Two amide conformers of the product **(14a)** were observed in a ratio of 3.6:1. The major conformer was identical to the major conformer observed in the Swern oxidation above. **14a** major conformer: 67%; ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 196.4, 172.7, 168.7, 136.0, 133.2, 129.5, 128.5, 47.1, 39.7. **14a** minor conformer: 18%; partial ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 195.8.

General Procedure for the CrO_2(O-*t*-Bu)$_2$ Oxidation of Resins 6 To Afford Resins 7. A solid-phase synthesis (SPS) flask was charged with malonamide resin **6** (approximately 0.2 mmol, 1.0 equiv). The resin was washed

with anhydrous CH_2Cl_2 (2 × 5 mL) and then suspended in CH_2Cl_2 (3 mL) with stirring. The oxidizing reagent was prepared as follows: A 25 mL three-necked round-bottomed flask was charged with *tert*-butyl alcohol (2 mmol, 10 equiv) and pyridine (3 mmol, 15 equiv) in CH_2Cl_2 (3 mL). The mixture was cooled in a CO_2/acetone bath, and CrO_2Cl_2 (1 mmol, 5 equiv) was added via syringe. After 5 min the reaction was warmed to room temperature. The reaction was red−orange in color and a precipitate formed. The heterogeneous mixture was transferred to the SPS flask containing the resin via a syringe with a large bore needle. The resin mixture darkened to a deep red−brown immediately upon addition of the oxidizing reagent. The reaction was stirred at room temperature for 28 h. The resin was filtered and washed consecutively with CH_2Cl_2 (4 × 10 mL), DMF (2 × 10 mL), MeOH (3 × 10 mL), and CH_2Cl_2 (5 × 10 mL) and then filtered and dried under vacuum to afford **7** as a brown resin. The resin loading was determined by ^{1}H NMR spectroscopy as described in the general procedures.[29] ^{13}C NMR spectra of the cleaved products were also acquired and showed a carbonyl resonance consistent with the desired products. Proton NMR spectra showed some broadening due to trace amounts of chromium in the sample.

Preparation and Cleavage of Resin 7a. The reaction was carried out using 0.19 mmol of resin **6a** to afford **7a** as a brown resin product (245.9 mg, 98% by wt). An aliquot (65.4 mg) was cleaved, and the loading was calculated (0.56 mmol/g, 75% of theoretical). One conformer of the cleaved product **(14a)** was observed and corresponded to the major conformer observed in the other oxidation procedures: HRMS calcd for (M + H) ($C_{11}H_{12}NO_4$) 222.0766, found 222.0754.

Preparation and Cleavage of Resin 7b. The reaction was carried out using 1.13 mmol of resin **6b** to afford **7b** as a brown resin product (1.50 g, 100% by wt). An aliquot (94.5 mg) was cleaved, and the loading was calculated (0.64 mmol/g, 86% of theoretical). Two amide conformers of the cleaved product **(14b)** were observed in a ratio of 3.2:1.0.

3-[(Phenylmethyl)(2-oxo-2-phenylethyl)]amino-3-oxopropionic Acid (14b). Major conformer: 66%; ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.92 (d, J = 7.8 Hz, 2H), 7.70 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.44−7.24 (m, 5H), 5.01 (s, 2H), 4.77 (s, 2H), 3.93 (s, 2H).

3-[(Phenylmethyl)(2-oxo-2-phenylethyl)]amino-3-oxopropionic Acid (14b). Minor conformer: 20%; ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.85 (d, J = 7.8 Hz, 2H), 7.70 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.44−7.24 (m, 5H), 4.91 (s, 2H), 4.78 (s, 2H), 3.69 (bs, 2H); HRMS calcd for (M + H) ($C_{18}H_{18}NO_4$) 312.1236, found 312.1229; partial MS (ion spray) 312 (100, M + H).

Isolation of 14b. An isolated sample was obtained by concentrating cleaved material (112.8 mg resin, loading of starting material **5** was 0.86 mmol/g) under a stream of nitrogen and then dissolving the residue in CH_2Cl_2 (0.5 mL) and washing with 0.5 M HCl (0.5 mL). The organic layer was dried ($MgSO_4$), filtered through a silica plug (1/4 in. in a glass pipet), and concentrated to afford the product as a yellow oil (16.5 mg, 63% based on the loading of **5**). Two conformers were observed (2.0:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.3 Hz, 2H, major), 7.84 (d, J = 6.4 Hz, 2H, minor), 7.65 (t, J = 6.7 Hz, 1H, minor), 7.62 (t, J = 6.7 Hz, 1H, major), 7.49 (t, J = 7.5 Hz, 2H, major and minor), 7.44−7.24 (m, 5H, major and minor), 4.87 (s, 2H, major), 4.72 (s, 2H, minor), 4.65 (s, 2H, major and minor), 3.63 (s, 2H, major), 3.33 (s, 2H, minor).

Preparation and Cleavage of Resin 7c. The reaction was carried out using 1.13 mmol of resin **6c** to afford **7c** as a brown resin product (1.47 g, 98% by wt). An aliquot (91.3 mg) was cleaved, and the loading was calculated (0.64 mmol/g, 84% of theoretical). Two amide conformers of the cleaved product **(14c)** were observed in a ratio of 2.8:1.0.

3-[(4-Methoxyphenylmethyl)(2-oxo-2-phenylethyl)]amino-3-oxo-propionic Acid (14c). Major conformer: 62%; ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.91 (d, J = 7.5 Hz, 2H), 7.70 (t, J = 7.8 Hz, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 4.98 (s, 2H), 4.72 (s, 2H), 3.94 (bs, 2H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 197.1, 173.8, 170.4, 159.0, 135.9, 133.7, 130.5, 129.5, 129.1, 128.6, 115.5, 56.0, 53.3, 53.0, 38.1.

3-[(4-Methoxyphenylmethyl)(2-oxo-2-phenylethyl)]amino-3-oxo-propionic Acid (14c). Minor conformer: 22%; ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.86 (d, J = 7.8 Hz, 2H), 7.70 (t, J = 7.8 Hz, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 8.3 Hz, 2H), 4.90 (s, 2H), 4.74 (s, 2H), 3.91 (s, 3H), 3.68 (bs, 2H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 196.0, 173.1, 170.9, 158.7, 136.2, 133.4, 129.6, 128.5, 127.6, 126.6, 115.3, 56.1, 53.6, 53.3, 37.9; HRMS calcd for (M + H) ($C_{19}H_{20}NO_5$) 342.1341, found 342.1324; partial MS (ion spray) 342 (100, M + H).

Isolation of 14c. An isolated sample was obtained by concentrating cleaved material (102.7 mg of resin, loading of starting material **5** was 0.987 mmol/g) under a stream of nitrogen and then dissolving the residue in CH_2Cl_2 (0.5 mL) and washing with 0.5 M HCl (0.5 mL). The organic layer was dried ($MgSO_4$), filtered through a silica plug (1/4 in. in a glass pipet), and concentrated to afford the product as a yellow oil (18.7 mg, 69% based on the loading of **5**). Two conformers were observed (1.8:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.1 Hz, 2H, major), 7.84 (d, J = 6.4 Hz, 2H, minor), 7.65 (t, J = 6.7 Hz, 1H, minor), 7.62 (t, J = 7.1 Hz, 1H, major), 7.46 (t, J = 7.5 Hz, 2H, major and minor), 7.15 (d, J = 7.8 Hz, 2H, minor), 7.11 (d, J = 8.1 Hz, 2H, major), 6.88 (d, J = 7.8 Hz, 2H, major), 6.82 (d, J = 8.1 Hz, 2H, minor), 4.79 (s, 2H, major), 4.62 (s, 4H, minor), 4.55 (s, 2H, major), 3.78 (s, 3H, major), 3.76 (s, 3H, minor), 3.62 (s, 2H, major), 3.28 (s, 2H, minor).

Preparation and Cleavage of Resin 7e. The oxidation was carried out with resin **6e** (2.5 g, 1.5 mmol) and freshly prepared CrO_2(O-*t*-Bu)$_2$ (12.5 mmol), according to the general procedure to afford **7e** as a brown resin (2.4 g, 96% by wt). An aliquot of resin (95.0 mg) was cleaved, and loading was determined by direct cleavage (0.55 mmol/g, 93%).

3-[(4-Chlorophenyl)(2-oxo-butyl)amino]-3-oxopropionic Acid (14e): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 4.64 (s, 2H), 3.50 (s, 2H), 2.61 (q, J = 7.2 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 209.0, 173.1,

169.1, 138.8, 136.5, 130.9, 128.6, 59.2, 38.9, 33.6, 6.96; HRMS calcd for (M + H) ($C_{13}H_{14}ClNO_4$) 284.0690, found 284.0731; partial MS (ion spray) 284 (100, M + H), 266 (19, M + H − H_2O).

Preparation and Cleavage of Resin 7f. The oxidation was carried out with resin **6f** (0.32 g, 0.2 mmol) and freshly prepared CrO_2(O-*t*-Bu)$_2$ (1.0 mmol), according to the general procedure to afford **7f** as a brown resin (0.30 g, 94%). An aliquot of resin (67.9 mg) was cleaved, and loading was determined by direct cleavage (0.42 mmol/g, 67%).

3-[(4-Chlorophenyl)(2-oxo-4-methylpentyl)amino]-3-oxo-propionic Acid (14f): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.48 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 7.5 Hz, 2H), 4.62 (s, 2H), 3.50 (s, 2H), 2.44 (d, J = 6.4 Hz, 2H), 2.15 (m, 1H), 0.94 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 208.4, 173.1, 169.2, 138.8, 136.5, 130.9, 128.6, 60.1, 49.0, 38.9, 25.4, 21.9; HRMS calcd for (M + H) ($C_{15}H_{18}ClNO_4$) 312.1003, found 312.1015.

Preparation and Cleavage of Resin 7g. The oxidation was carried out with resin **6g** (0.25 g, 0.2 mmol) and freshly prepared CrO_2(O-*t*-Bu)$_2$ (1.0 mmol), according to the general procedure to afford **7g** as a brown resin (0.24 g, 96% by wt). An aliquot of resin (76.9 mg) was cleaved, and loading was determined by direct cleavage (0.53 mmol/g, 65%).

3-[(4-Methoxyphenyl)(2-oxo-butyl)amino]-3-oxo-propionic Acid (14g): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.30 (d, J = 7.5 Hz, 2H), 7.01 (d, J = 7.5 Hz, 2H), 4.64 (s, 2H), 3.89 (s, 3H), 3.50 (s, 2H), 2.60 (q, J = 6.3 Hz, 2H), 1.14 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 209.3, 173.4, 169.8, 160.0, 133.4, 128.4, 115.8, 59.5, 55.7, 38.7, 33.6, 7.00; HRMS calcd for (M + H) ($C_{14}H_{17}NO_5$) 280.1185, found 280.1221.

Preparation and Cleavage of Resin 7h. The oxidation was carried out with resin **6h** (0.35 g, 0.2 mmol) and freshly prepared CrO_2(O-*t*-Bu)$_2$ (1.0 mmol), according to the general procedure to afford **7h** as a brown resin (0.33 g, 94% by wt). An aliquot of resin (54.9 mg) was cleaved, and loading was determined by direct cleavage (0.45 mmol/g, 88%).

3-[(3,5-Dimethylphenyl)(2-oxo-butyl)amino]-3-oxo-propanoic Acid (14h): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.11 (s, 1H), 6.92 (s, 2H), 4.64 (s, 2H), 3.52 (s, 2H), 2.61 (q, J = 7.0 Hz, 2H), 2.34 (s, 6H), 1.15 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 209.2, 173.5, 169.5, 141.0, 140.1, 131.7, 124.2, 59.3, 38.6, 33.6, 20.6, 7.00; HRMS calcd for (M + H) ($C_{15}H_{19}NO_4$) 278.1392, found 278.1387.

Preparation and Cleavage of Resin 7i. The oxidation was carried out with approximately 500 mg of resin **6i** and freshly prepared CrO_2(O-*t*-Bu)$_2$ to afford the product **7i** as a brown resin. An aliquot (90.7 mg) was cleaved, and the loading was calculated using the methyl protons of the isopropyl group (0.69 mmol/g, 79% of theoretical).

3-[(2-Methylethyl)(2-oxo-2-phenylethyl)amino]-3-oxo-propanoic Acid (14i): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 8.00 (d, J = 7.2 Hz, 2H), 7.78−7.70 (m, 1H), 7.63−7.51 (m, 2H), 4.87 (s, 2H), 4.26 (m, 1H), 3.87 (bs, 2H), 1.29 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 195.9, 173.7, 169.3, 135.6, 133.6, 129.3, 128.4, 51.0, 48.0, 37.2, 19.9; HRMS calcd for (M + H − CO_2)($C_{13}H_{17}NO_2$) 264.1338, found 264.1339.

Preparation and Cleavage of Resin 7j. The reaction was carried out using 0.50 mmol of starting material resin **6j** to afford **7j** as a dark brown resin product (0.91 g, 104% by wt). An aliquot (95.2 mg) was cleaved, and the loading was calculated using the phenyl protons in the product (0.38 mmol/g, 61% of theoretical). One product was observed and characterized.

3-[(2-Ethylbutyl)[(1-methyl-2-oxo-2-phenyl)ethyl]amino]-3-oxo-propanoic Acid (14j): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.55 (m, 3H), 7.47 (m, 2H), 4.72 (q, J = 6.4 Hz, 1H), 3.96 (bs, 2H), 3.55 (m, 2H), 1.62 (m, 1H), 1.40 (m, 4H), 1.38 (bd, J = 6.2 Hz, 3H), 0.90 (m, 6H); HRMS calcd for (M + H) ($C_{18}H_{26}NO_4$) 320.1862, found 320.1871.

Preparation and Cleavage of Resin 7k. The reaction was carried out using 0.50 mmol of starting material resin **6k** to afford **7k** as a dark brown resin product (1.00 g, 98% by wt). An aliquot (86.8 mg) was cleaved, and the loading was calculated using the phenyl protons in the product (0.55 mmol/g, 98% of theoretical). One product was observed and characterized.

3-[(2-Ethylbutyl)(2-oxo-1,2-diphenylethyl)amino]-3-oxo-propanoic Acid (14k): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.69 (m, 2H), 7.48 (m, 2H), 7.36 (m, 4H), 7.25 (m, 2H), 6.52 (s, 1H), 3.88 (bs, 2H), 3.36 (d, J = 16.2 Hz, 1H), 3.30 (d, J = 16.8 Hz, 1H), 1.14 (m, 5H), 0.68 (t, J = 7.4 Hz, 3H), 0.60 (t, J = 7.3 Hz, 3H); HRMS calcd for (M + H) ($C_{23}H_{28}NO_4$) 382.2018, found 382.2015.

General Procedure for Cyclization of Resins 7 To Afford Resins 8. Resin **7** (75 μmol) was suspended in dry THF under N_2 and cooled to −78 °C. $ZnCl_2$/THF (0.5 M, 75 μmol, 150 μL) and LHMDS/THF (1 M, 150 μmol, 150 μL) were added. Although LDA could also be used, LHMDS gave superior results. The reaction was agitated and allowed to warm to 0 °C. Agitation was continued at 0 °C for an additional 1.5−2 h. The reaction was quenched with aqueous NH_4Cl, filtered, washed with THF, MeOH, MeOH/H_2O 1:1, MeOH, and CH_2Cl_2, and dried. An aliquot of resin was cleaved, and the loading was calculated by ^{1}H NMR spectroscopy as described in the general procedures.

Preparation of Resin 8b and Cleavage To Afford 9b. The reaction was carried out using 305 mg of resin **7b** to afford the product **8b** as a brown resin (318 mg). An aliquot (113.5 mg) was cleaved, and the loading was calculated by NMR integration of the phenyl protons (0.53 mmol/g, 93% of theoretical).

2,5-Dihydro-4-phenyl-1-phenylmethyl-2-oxo-1*H*-pyrrole-3-carboxylic Acid (9b): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.11−7.74 (m, 10H), 4.82 (s, 2H), 4.47 (s, 2H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 179.3, 172.6, 171.2, 133.8, 132.9, 131.1, 129.9, 129.8, 129.5, 128.9, 128.7, 128.3, 55.3, 49.9; HRMS calcd for (M + H − CO_2) ($C_{18}H_{15}NO_3$) 250.1232, found: 250.1229; partial MS (ion spray) 499 (58, 2M + H − 2CO_2), 250 (100, M + H − CO_2).

Preparation of Resin 8c and Cleavage To Afford 9c. The reaction was carried out using 202 mg of resin **7c** to afford the product **8c** as a brown resin (318 mg). An aliquot

(101.7 mg) was cleaved, and the loading was calculated using the phenyl protons (0.61 mmol/g, 94% of theoretical).

2,5-Dihydro-1-(4-methoxyphenylmethyl)-2-oxo-4-phenyl-1*H*-pyrrole-3-carboxylic Acid (9c): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.11−7.74 (m, 10H), 4.76 (s, 2H), 4.45 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 179.3, 171.9, 171.0, 158.8, 133.6, 130.5, 130.1, 129.8, 129.4, 128.9, 128.7, 128.3, 55.9, 55.8, 49.9; HRMS calcd for (M + H − CO_2) ($C_{19}H_{17}NO_4$) 280.1338, found 280.1339; partial MS (ion spray) 559 (89, 2M + H − 2CO_2), 280 (100, M + H − CO_2).

Preparation and Cleavage of Resin 8e. The cyclization was carried out with resin **7e** (75 μmol), $ZnCl_2$/THF (0.5 M, 75 μmol, 150 μL), and LHMDS/THF (1 M, 150 μmol, 150 μL) according to the general procedure to afford resin **8e** (78.6 mg). The resin was cleaved, and the loading was determined by direct cleavage (0.45 mmol/g, 82%).

1-(4-Chlorophenyl)-5-ethyl-2,5-dihydro-2-oxo-1*H*-pyrrole-3-carboxylic Acid (9e): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.43 (bs, 5H), 4.71 (s, 2H), 3.12 (bq, J = 6.4 Hz, 2H), 1.33 (bt, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 180.2, 170.3, 133.9, 133.7, 131.1, 129.9, 123.0, 119.1, 56.0, 23.7, 11.9; HRMS calcd for (M + H) ($C_{13}H_{12}ClNO_3$) 266.0584, found 266.0566.

Isolation of 9e. An isolated sample was obtained by concentrating cleaved material (78.6 mg of resin, loading of starting material **5** was 0.94 mmol/g) under a stream of nitrogen to afford the product as a yellow oil (9.0 mg, 53% based on the loading of **5**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.9 Hz, 2H), 7.40 (d, J = 8.9 Hz, 2H), 4.52 (s, 2H), 3.13 (q, J = 7.5 Hz, 2H), 1.30 (t, J = 7.5 Hz, 3H); partial MS (ion spray) 266 (100, M+H), 248 (77, M + H − H_2O).

Preparation and Cleavage of Resin 8g. The cyclization was carried out with resin **7g** (62.5 μmol), $ZnCl_2$/THF (0.5 M, 62.5 μmol, 125 μL), and LHMDS/THF (1 M, 125 μmol, 125 μL) according to the general procedure to afford resin **8g** (144.2 mg). The resin was cleaved, and the loading was determined by direct cleavage (0.40 mmol/g, 85%).

5-Ethyl-2,5-dihydro-1-(4-methoxyphenyl)-2-oxo-1*H*-pyrrole-3-carboxylic Acid (9g): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.35 (d, J = 7.1 Hz, 2H), 7.06 (d, J = 7.4 Hz, 2H), 4.70 (s, 2H), 3.92 (s, 3H), 3.14 (q, J = 5.8 Hz, 2H), 1.33 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 180.4, 170.7, 158.7, 128.2, 125.3, 115.4, 57.5, 55.9, 53.1, 53.1, 23.5, 11.7; HRMS calcd for (M + H − CO_2) ($C_{14}H_{15}NO_4$) 218.1181, found 218.1205.

Preparation and Cleavage of Resin 8h. Resin **7h** (62.5 μmol) was suspended in dry THF under N_2 and cooled to −78 °C. $ZnCl_2$/THF (0.5 M, 62.5 μmol, 125 μL) and LHMDS/THF (1 M, 125 μmol, 125 μL) were added. Reaction was allowed to warm to 0 °C and agitated for 2 h. The reaction was quenched with aqueous NH_4Cl, filtered, washed with THF, MeOH, MeOH/H_2O 1:1, MeOH, and CH_2Cl_2, and dried. The resin (134.6 mg) was cleaved and assayed by direct cleavage (0.41 mmol/g, 90%).

5-Ethyl-2,5-dihydro-1-(3,5-dimethylphenyl)-2-oxo-1*H*-pyrrole-3-carboxylic Acid (9h): ^{1}H NMR: (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.06 (s, 1H), 7.00 (s, 1H), 6.79 (s,1H), 4.71 (s, 2H), 2.34 (s, 6H), 1.33 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 173.4, 169.7, 140.4, 130.4, 124.1, 121.0, 57.5, 53.1, 36.3, 27.1, 20.6, 11.7; HRMS calcd for (M + H − CO_2) ($C_{15}H_{17}NO_3$) 216.1388, found 216.1380.

Preparation of Resin 8i and Cleavage To Afford 9i. The reaction was carried out using approximately 360 mg of resin **7i** to afford the product **8i** as a brown resin product. An aliquot (104.8 mg) was cleaved, and the loading was calculated by NMR integration of the methyl protons of the isopropyl group (0.48 mmol/g, 69% of theoretical).

1-(2-Methylethyl)-2,5-dihydro-2-oxo-5-phenyl-1*H*-pyrrole-3-carboxylic Acid (9i): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.35−7.69 (m, 5H), 4.62 and 4.50−4.62 (s and m, 3H), 1.40 (d, J = 4.8 Hz, 6H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 179.6, 169.2, 158.2, 131.3, 129.9, 127.7, 125.9, 54.9, 49.7, 18.6. HRMS calcd for (M + H − CO_2) ($C_{13}H_{15}NO$): 202.1232, found 202.1209.

Preparation and Cleavage of Resin 8j. The cyclization was carried out using resin **7j** (227 mg, 79 μmol), $ZnCl_2$/THF (0.5 M, 200 μmol, 400 μL), and LDA/THF (0.43 M, 150 μmol, 350 μL) according to the general procedure to afford resin **8j** (235 mg, 66 μmol). An aliquot of resin (78.6 mg) was cleaved, and the loading was determined (0.14 mmol/g, 38% of theoretical).

1-(2-Ethylbutyl)-2,5-dihydro-5-methylene-2-oxo-4-phenyl-1*H*-pyrrole-3-carboxylic Acid (16j): ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.30−7.64 (m, 5H), 5.92 (s, 1H), 5.61 (s, 1H), 3.77 (bs, 2H), 1.74 (bs, 1H), 1.39 (bs, 4H), 0.94 (bs, 6H); ^{13}C NMR (100 MHz, 1:1 TFA:$CDCl_3$) δ 172.9, 170.2, 168.5, 159.1, 131.5, 130.0, 129.5, 128.4, 114.2, 93.2, 44.7, 40.2, 23.1, 9.8; HRMS calcd for (M + H − CO_2) ($C_{17}H_{22}NO$) 256.1701, found 256.1701.

Preparation and Cleavage of Resin 8k. The cyclization was carried out using resin **7k** (224 mg, 114 μmol), $ZnCl_2$/THF (0.5 M, 270 μmol, 550 μL), and LDA/THF (0.43 M, 200 μmol, 470 μL) according to the general procedure to afford resin **8k** (239 mg, 127 μmol). An aliquot of resin (115.1 mg) was cleaved, and the loading was determined (0.42 mmol/g, 80% of theoretical).

1-(2-Ethylbutyl)-2,5-dihydro-4,5-diphenyl-2-oxo-4-phenyl-1*H*-pyrrole-3-carboxylic Acid (9k) and **1-(2-Ethylbutyl)-2,5-dihydro-5-hydroxy-4,5-diphenyl-2-oxo-4-phenyl-1*H*-pyrrole-3-carboxylic Acid (15k):** ^{1}H NMR (400 MHz, 1:1 TFA:$CDCl_3$) δ 7.00−7.65 (m, 10H), 5.27 (s, 1H, **9k**), 3.62 (m, 1H), 3.48 (m, 1H), 2.95 (m, 1H), 2.81 (m, 1H), 1.40 (m, 1H), 1.23 (m, 4H), 0.96−0.62 (m, 6H); HRMS calcd for **9k** (M + H − CO_2) ($C_{17}H_{22}NO$) 320.2014, found 320.2019; HRMS calcd for **15k** (M + H) ($C_{23}H_{26}NO_4$) 380.1862, found 380.1905.

Preparation of 17. Resin **8k** (115 mg, 48 μmol) was cleaved using TFA/$CDCl_3$, and the product was concentrated under a stream of nitrogen. The residue was dissolved in CH_2Cl_2 (5 mL), and 1,1′-carbonyldiimidazole (50 mg, 308 μmol) was added. The mixture was stirred at ambient temperature for 18 h, and excess methanol (1 mL) was added. The reaction mixture was stirred for 3 days at ambient temperature. Additional CH_2Cl_2 (1.5 mL) was added, and the resulting solution was washed with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 1.5 mL),

and the combined extracts were concentrated under a stream of nitrogen. The crude product was purified by silica gel chromatography using 5% CH_2Cl_2, 50% EtOAc in hexanes, to give a water white liquid (7 mg, 17 μmol).

Methyl 1-(2-Ethylbutyl)-2,5-dihydro-5-hydroxy-4,5-diphenyl-2-oxo-4-phenyl-1*H*-pyrrole-3-carboxylate (17): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−7.44 (m, 10H), 3.80 (s, 3H), 3.31(dd, J = 14.4, 7.2 Hz, 1H), 2.73 (dd, J = 14.4, 7.2 Hz, 1H), 1.73 (bs, 2H), 1.31 (hextet, J = 6.4 Hz, 1H), 1.14−1.26 (m, 2H), 0.77 (t, J = 7.2 Hz, 3H), 0.68 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.2, 160.4, 136.3, 130.4, 130.1, 129.1, 128.9, 128.9, 128.4, 126.3, 125.7, 93.0, 52.7, 43.6, 39.5, 23.7, 23.6, 10.79, 10.71; HRMS calcd for (M + H) ($C_{24}H_{28}NO_4$) 394.2018, found 394.2022.

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Supporting Information Available. Representative spectra of cleaved products in $CDCl_3$:TFA: **9c**, **14c**. Representative spectra of isolated products in $CDCl_3$: **9e**, **14b, 14c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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