A Spiroisoxazolinoproline-Based Amino Acid Scaffold for Solid Phase and One-Bead−One-Compound Library Synthesis

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Received June 30, 2006

An efficient, multigram synthesis of a spiroisoxazolinoproline-based amino acid, **7**, requiring minimal purification, delivering good cis:trans diastereoselectivity (∼1:4), and providing good yields is reported. Surface-bound studies of the reduction of an arylnitro group in the presence of an isoxazoline ring with tin(II) dichloride dihydrate were undertaken to confirm the stability of the isoxazoline ring. Full derivitization of this spiroisoxazolinoproline-based amino acid scaffold was performed during the synthesis of a sample library with high yields and high purity that validated the efficiency of the chemistry that was employed in resin-bound library synthesis. A 129 600 member one-bead−one-compound (OBOC) library based on the scaffold **7** was synthesized utilizing a dual amino acid encoding method and bifunctionalization of TentaGel resin.

Introduction

Unnatural amino acid derivatives are attractive building blocks for medicinal chemistry due to their intrinsic bioactivity and biostability. In the case of proline and proline analogues, which have a well-documented history of biological activity,[1−4] the utility is augmented by a versatile heterocyclic structure. Isoxazoline rings also have a rich history in drug discovery.[5−7] Additionally, amino acid scaffolds readily allow for the introduction of diversity elements containing other structures known to invoke biological responses and are fast becoming a staple in drug discovery.[8−12] The goal of our work here is to combine all of these facets to provide a biologically relevant scaffold that allows for the incorporation of diversity elements that increase biological activity in targeted enzymatic or protein systems. To this end, we have expanded our previous work in this area[13] and report here a spiroisoxazolinoproline-based amino acid derivative (**7**, Scheme 1) that has three diversity points that are spatially arranged by the spirocyclic nature of the scaffolding such that the diversity elements are precisely displayed. Trifunctional amino acid **7** presents each diversification point in such a way that construction proceeds easily and efficiently.

Peptide-based combinatorial chemistry combined with one-bead−one-compound methods for solid-phase organic synthesis is an important tool in the drug discovery process. However, peptide inhibitors or activators of enzymes and proteins are limited in their use because they are subject to proteolysis, they are not orally active, and they are not able to cross cell membranes. Nonnatural amino acid-based peptide inhibitors or activators compensate for this, but still suffer from the fact that peptides make poor drug candidates for these and other reasons.[14] Because of this, we sought to develop a small-molecule, proline-based library rather than a traditional peptide library. Although one-bead−one-compound, small-molecule library synthesis accommodates diverse methodology,[15−17] we needed an encoding method that would allow for structural isomers and amino acids with similar or identical masses. Hence, mass-tag encoding strategies were not an option. Edman degradation encoding methods are reliable but encounter difficulties in that only a limited number of retention times are resolvable in a sequencing trace. However, a binary encoding strategy allows any diversity element to be encoded by two amino acids with easily distinguishable retention times.[18]

Any new library synthesis requires validating studies to establish that the chemistry performs reliably during library synthesis. Our goal was to develop an efficient synthesis of a highly functionalized, rigid, spiroisoxazolinoproline derivative that could be prepared in multigram quantities and that facilitates library synthesis by employing reliable chemical transformations. We report herein the development of these methods in a sample library synthesis and subsequent application in the preparation of a 129 600-member, on-bead, encoded library that has shown promising preliminary results in several biological systems.

Results and Discussion

Our synthetic efforts to deliver the desired scaffolding molecule began with a reworking of our previous synthetic efforts[13] to increase the overall efficiency of each synthetic step. Specifically, during the 1,3-dipolar cycloaddition step, it has been our experience that the presence of a free carboxylic acid causes lower yields. To circumvent this

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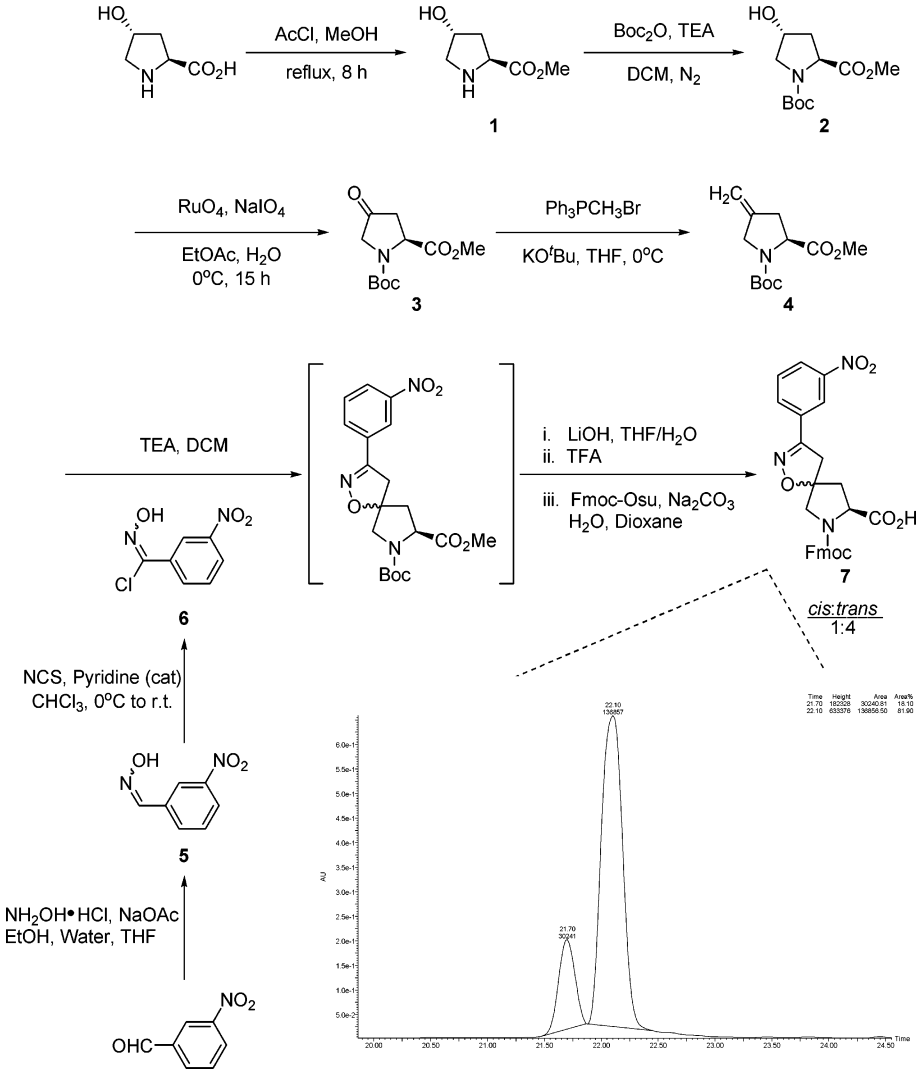
10.1021/cc060090p CCC: $37.00
Published on Web 11/15/2006

Scheme 1. Synthesis of Scaffold Material



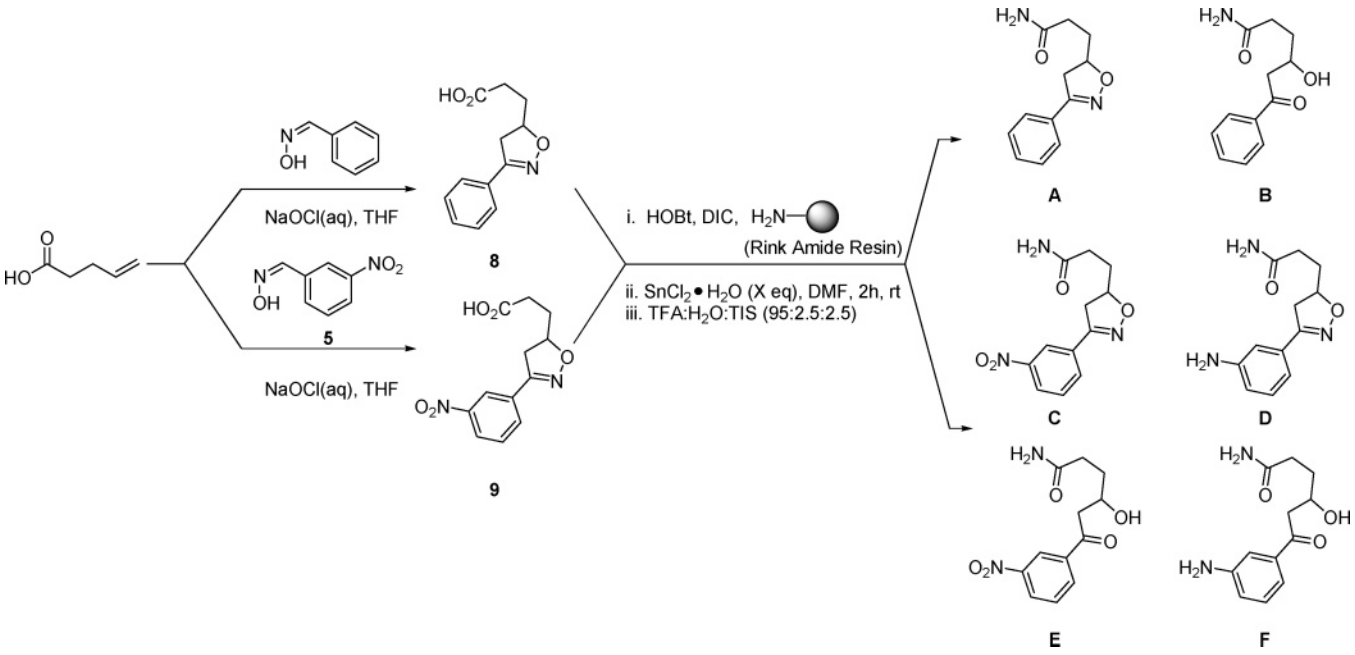
problem, *trans*-4-hydroxy-L-proline was methyl-ester-protected, as depicted in Scheme 1, by treatment with acetyl chloride in methanol.[19] Without the need for purification, the secondary amine of **1** was Boc-protected by treatment with Boc anhydride in the presence of triethylamine.[20] Again, without purification, ruthenium tetroxide oxidation of the secondary alcohol in crude **2** was carried out in the presence of sodium periodate.[21] The biphasic reaction was yellow before **2** was added; with the addition of **2**, the reaction solution eventually turned to green/black, at which time TLC indicated that the reaction had gone to completion. Standard workup delivered **3**, which also required no further purification. It should also be noted that our protocol for this oxidation replaced carbon tetrachloride and ethanol with ethyl acetate to form the biphasic reaction mixture. Wittig olefination of crude **3** was undertaken according to literature procedures[22] to deliver **4** in good yield. Column chromatographic purification was required at this point and gave **4** in a 58% overall yield from *trans*-4-hydroxy-L-proline.

Oxime **5** was synthesized and subsequently converted to **6** by *N*-chlorosuccinimide treatment. In situ nitrile oxide formation from **6** with triethylamine and subsequent 1,3-dipolar cycloaddition to the C═C double bond of **4** delivered a 1:4::cis:trans diastereomeric mixture of cycloadducts. Although it is possible to perform the 1,3-dipolar cycloaddition straight from the oxime in the presence of sodium hypochlorite, the large-scale use of a bleach solution (the common delivery means for sodium hypochlorite) would require volumes that were unreasonable for standard lab work. The use of the chlorooxime with triethylamine allowed for a more concentrated reaction mixture and an improved yield, as well as shorter reaction times.

As outlined in the Experimental Section, this crude reaction mixture was taken through a series of steps without isolating any intermediates because it proved possible to achieve moderate purification by simply extracting into aqueous base and then aqueous acid once the methyl ester had been hydrolyzed to the free carboxylic acid. Boc deprotection followed by Fmoc protection proceeded smoothly to deliver **7** as a mixture of diastereomers (1:4::cis:trans) after column purification.[13]

Although it was possible to separate the diastereomers by reversed-phase HPLC, as illustrated by the LC trace in Scheme 1, separation was not possible by standard column chromatography. Consequently, this diastereomeric mixture was employed in the ensuing library syntheses. It should be noted that these spirocyclic diastereomers are easiest to separate in the Boc-protected form. Therefore, once a lead

Scheme 2. Synthetic Route for the Study of Arylnitro Reduction in the Presence of an Isoxazoline Ring



compound is identified via on-bead screening, each diastereomer will be considered individually in follow-up assays, and flash chromatography will be utilized to separate the Boc-protected diastereomer; these will then be carried through to the final Fmoc-protected form.

Before derivative and library syntheses were undertaken, there remained a question regarding the stability of the isoxazoline ring under the conditions required to reduce the arylnitro group. Indeed, literature protocols for isoxazoline N—O bond cleavage upon treatment with metal-based reducing agents[23−25] raised a concern that exposure of **7** to tin(II) dichloride dihydrate would effect an unwanted isoxazoline ring cleavage. To address this issue, two model compounds, **8** and **9**, were prepared according to Scheme 2 by performing 1,3-dipolar cycloaddition reactions between 4-pentenoic acid and two oximes: benzaldehyde oxime and **5**, respectively. The resulting cycloadducts differ only in that the aryl group of **9** is 3-nitro-substituted. As a result, these two systems afforded an effective means by which to study the reduction of the arylnitro group in the presence of an isoxazoline ring, since compound **8** contains only an isoxazoline ring (and no arylnitro group), and compound **9** contains both an isoxazoline ring and an arylnitro group. To conduct these experiments under librarylike conditions, cycloadducts **8** and **9** were individually coupled to Rink resin and subjected to varying equivalents of tin(II) dichloride dihydrate. Other than varying the equivalents of the reducing agent, all reaction conditions were held constant (2 h at room temperature in DMF). Workup consisted of removing the tin(II) dichloride dihydrate from the resin by washing. The resulting resin was subjected to cleavage conditions (TFA/H_2O/TIS) to liberate potential products **A**−**F**, and the crude cleavage mixture was analyzed by LC/MS. We were pleased to discover that under no conditions were isoxazoline ring cleavage products detected; products **B**, **E**, and **F** were not observed. Indeed, very specific conditions for the solid-phase reduction of an arylnitro moiety could be arrived at using the data gathered from this LC/MS study as presented in Table 1. Namely, 30 equiv of tin(II) dichloride dihydrate in DMF for 2 h at room temperature completely reduced the nitro group of resin-bound **9** but had no effect on resin-bound **8**. Application of these conditions delivered the desired product in all subsequent library syntheses.

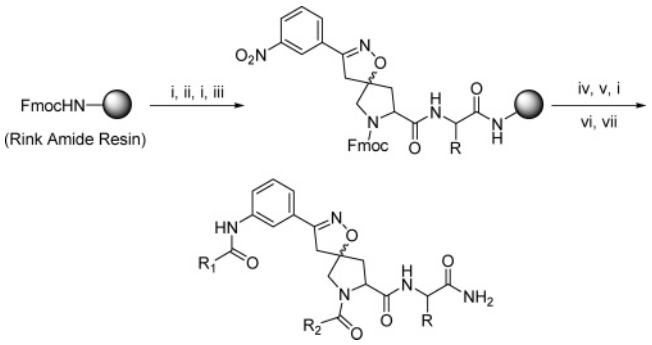
Table 1. Reduction Studies of Isoxazoline with $SnCl_2 \cdot 2H_2O$ on Solid Phase

equiv $SnCl_2 \cdot 2H_2O$	amt C remaining (%)[a]	amt D formed (%)[a]
1	99.9	0.1
5	98.8	1.2
10	70.2	29.8
15	28.4	71.6
20	13.9	86.2
21	7.8	92.2
22	6.6	93.4
23	4.5	95.5
24	3.6	96.4
25	1.4	98.6
26	0.6	99.4
27	0	100
28	0	100
29	0	100
30	0	100
50	0	100
100	0	100

[a] Percentages of C and D based on LC/MS integrations of the peaks of interest.

With this important question answered, we turned our attention to the synthesis of several example compounds in a small sample library that would be representative of the resin-bound molecules to be found in our one-bead−one-compound library.[26−28] We thus set out to prepare a sample library of 20 compounds according to Scheme 3. Standard procedures amenable to solid-phase work (i.e., amino acid coupling, N-acylation, etc.) were employed to construct these compounds. With the exception of **10h**, all compounds were obtained in high yield and crude purity as seen in Table 2. To fully

Scheme 3. Synthetic Route for the Derivatization of Scaffolding Molecule[a]



[a] Reagents and conditions: (i) 20% piperidine in DMF, 2 × 10 min; (ii) Fmoc-R−OH, HOBt, DIC, DMF; (iii) mixture of **7a** and **b** (4:1), HOBt, DIC, DMF; (iv) $SnCl_2 \cdot 2H_2O$ (30 equiv), DMF, 2h; (v) R_1-CO_2H, HOBt, DIC, DMF; (vi) R_2-CO_2H, HOBt, DIC, DMF; (vii) TFA/H_2O/TIS (95:2.5:2.5) or TFA/phenol/TIS/H_2O/EDT (90/5/2/2/1, v/w/v/v/v).

characterize each of the compounds, they were subjected to HPLC purification to deliver each compound in 95% purity. Analyses performed on each compound showed, as was expected, that there were great similarities in the spectral data obtained. ^{1}H NMR and ^{13}C NMR interpretations of these compounds were complicated, because they were mixtures of diastereomers with added rotational isomerism.[29] It was possible to separate some of these diastereomers by HPLC methods, and **10e** was subjected to this separation for illustrative purposes in accordance with literature precedence.[26,30,31] The major and minor diastereomers of **10e** were isolated, as seen in Figure 1, and the NMR data (see Supporting Information) illustrated the different characteristics of each isomer. Regardless of whether separated into individual diastereomers, scaffold similarities were easily detected in these compounds in the NMR, and in most cases, it was possible to identify appropriate functional group peaks when they stood apart from the scaffolding background peaks (see the Supporting Information for NMR spectra). Most importantly, when dealing with compounds with this level of complexity, the HRMS data reliably verified each structure. As mentioned before, compound **10h** was obtained in lower yield than the other compounds and was difficult to purify by HPLC because its solubility was low in all solvents tested. After attempts at HPLC purification, insufficient material was available to obtain a clean ^{1}H NMR, and ^{13}C NMR data was wholly unattainable. This compound was, however, characterized by LC/MS, HRMS, and IR.

With this success in synthesizing a sample library containing compounds that mimicked our desired library molecules, we set out to prepare a peptide-encoded, one-bead−one-compound, small-molecule library. The overall synthesis is presented in Scheme 4 and was initiated by the swelling of TentaGel resin in water for 48 h, followed by Fmoc-OSu treatment to cause bifunctionalization of the resin beads. Bifunctionalization was induced by a literature procedure developed in the Lam lab.[17]

First, surface amines were Fmoc-protected, and in a second step, the inner core amines were orthogonally Boc-protected to finalize bifunctionalization. Next, we introduced a solubilizing piperazine-based linker on the outer layer of the bead that was intended to solve the solubility problems encountered with compounds such as **10h**.[32−34] This linker was Fmoc-protected, whereas the interior of the bead would be orthogonally protected by a Boc group to accommodate the eventual construction of the encoding tag. The piperazine moiety was added to help the solubility of the surface molecules in biological studies by making these molecules more water-soluble. To accomplish this, 2-bromoacetic acid was coupled to the outer layer amines, and piperazine was subsequently employed in bromide displacement.

With the solubilizing linker in place, we turned to the encoding tag synthesis. A solid-phase peptide coupling was used to introduce a semiorthogonally protected lysine, Boc-Lys(Dde)-OH, that would encode for R_2. Next, Boc-Phe(4-NO_2)−OH was coupled to the encoding tag so that reduction of the arylnitro group on the scaffolding molecule and subsequent N-acylation (R_1 introduction) could be encoded by the arylnitro group on this phenylalanine derivative. Retention times for these analogs had been previously determined by Edman degradation sequencing.[18] The encoding tag synthesis was then completed by coupling a combination of two commercially available Boc-protected amino acids. Since their relative reactivities had been determined,[18] defined quantities of their respective stock solutions could be coupled such that Edman degradation sequencing would produce two easily distinguishable signals. These two signals would subsequently reveal the amino acid diversity element of the outer layer target molecule. By this method, it is possible to couple any amino acid diversity element to the outer layer target molecule without prior knowledge of its specific retention time, which allows for far greater amino acid diversity in library synthesis. At the completion of encoding tag synthesis, the resin remained separated into different vessels, and Fmoc deprotection was performed. The testing amino acid diversity element (X in Scheme 4) was then coupled to the secondary amine of the piperazine-containing solubilizing linker. Library synthesis was continued by pooling the resin and subsequent coupling of scaffold **7** to the amino acid diversity element, followed by reduction of the aryl nitro group. The resin was then divided into 30 plastic columns, and R_1-CO_2H was coupled to the target molecule's aniline moiety as well as to the encoding tag. Pooling and Fmoc (proline secondary amine) as well as Dde (ϵ-Lys amine) groups were simultaneously removed with 2% hydrazine in DMF. The resin was split into 45 plastic columns, and the final diversity element, R_2-CO_2H, was coupled to the target molecule and the encoding tag. Finally, a global deprotection was performed to remove all of the remaining acid-sensitive protecting groups to deliver the target library, which was readily sequencable by Edman degradation (an example is presented in the Supporting Information). The library containing 129 600 unique compounds was thoroughly washed, placed in 0.1% sodium azide in PBS buffer, and stored in a refrigerator for future assaying experiments. This OBOC library will be subject to biological assay on-bead, and subsequent Edman degradation techniques will be employed to reveal the identity of hit molecules. Once identified, hits will be resynthesized on resin via a cleavable linker strategy or in solution phase.

Table 2. Scaffold Diversity Elements, Purity, and Yield[a]

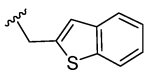
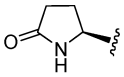
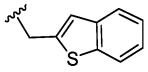
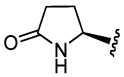
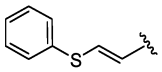
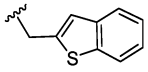
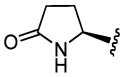
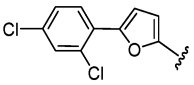
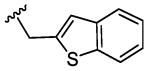
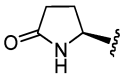
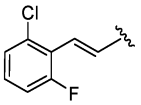
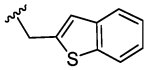
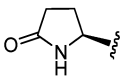
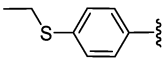
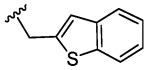
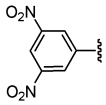
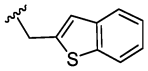
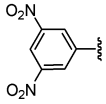
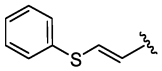
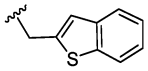
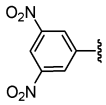
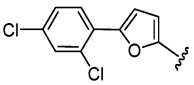
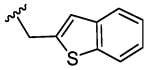
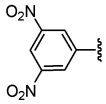
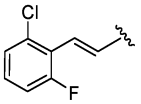
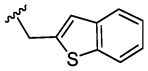
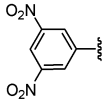
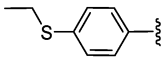
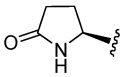
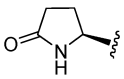
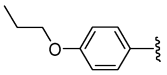
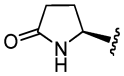
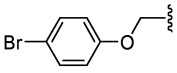
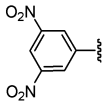
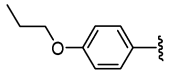
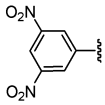
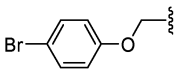
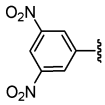
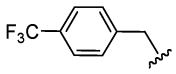
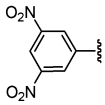
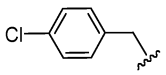
Entry	R	R_1	R_2	Crude Yield (%)[a]	Crude Purity (%)[b]
10a				83	91
10b				92	93
10c				85	84
10d				91	88
10e				89	91
10f				86	94
10g				82	90
10h				56	84
10i				87	98
10j				83	96
10k				85	95
10l				84	95
10m				91	96
10n				82	98
10o				87	97
10p				86	98

Table 2 (Continued)

Entry	R	R_1	R_2	Crude Yield (%)[a]	Crude Purity (%)[b]
10q				89	93
10r				86	98
10s				82	93
10t				84	96

Conclusions

In summary, we have described the multigram synthesis of a trifunctional spiroisoxazolinoproline-based scaffold **7** that requires minimal purification to deliver the desired product in high overall yield (31% from *trans*-4-hydroxy-L-proline). We also performed solid-phase arylnitro reduction studies to confirm the stability of an isoxazole ring as well as to provide optimized conditions for this tin chloride reduction. Because the goal of this work was to create a one-bead−one-compound discovery library based on scaffold **7**, we synthesized a small sample library of small-molecule derivatives (**10a**−**t**) to validate the chemical methods to be employed during library construction. These example compounds were purified and obtained in high yield and good crude purity; they were fully characterized. With these data in hand, a dual amino acid encoding system was employed in the synthesis of a 129 600-member, one-bead−one-compound library that is readily sequencable by Edman degradation. Applications of this library in biological assays will be reported in due course.

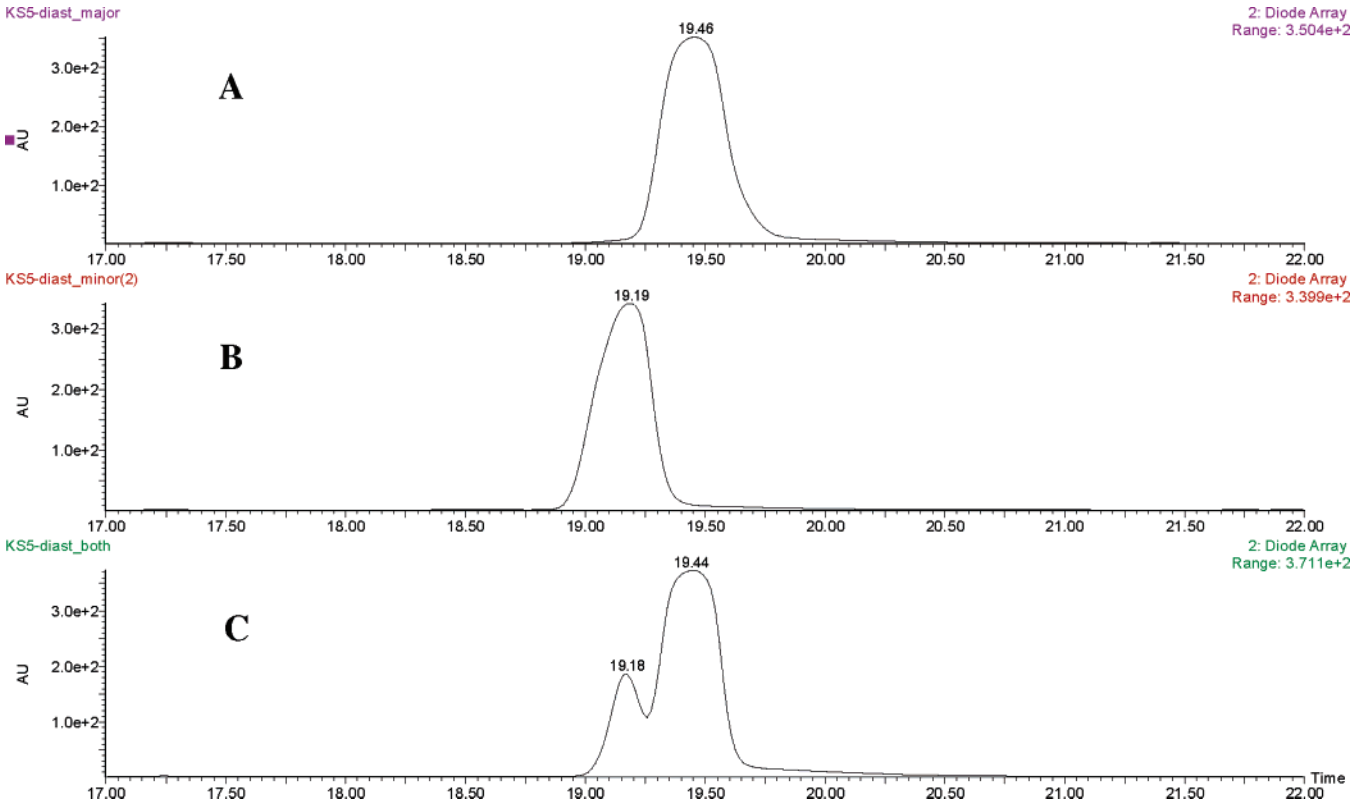
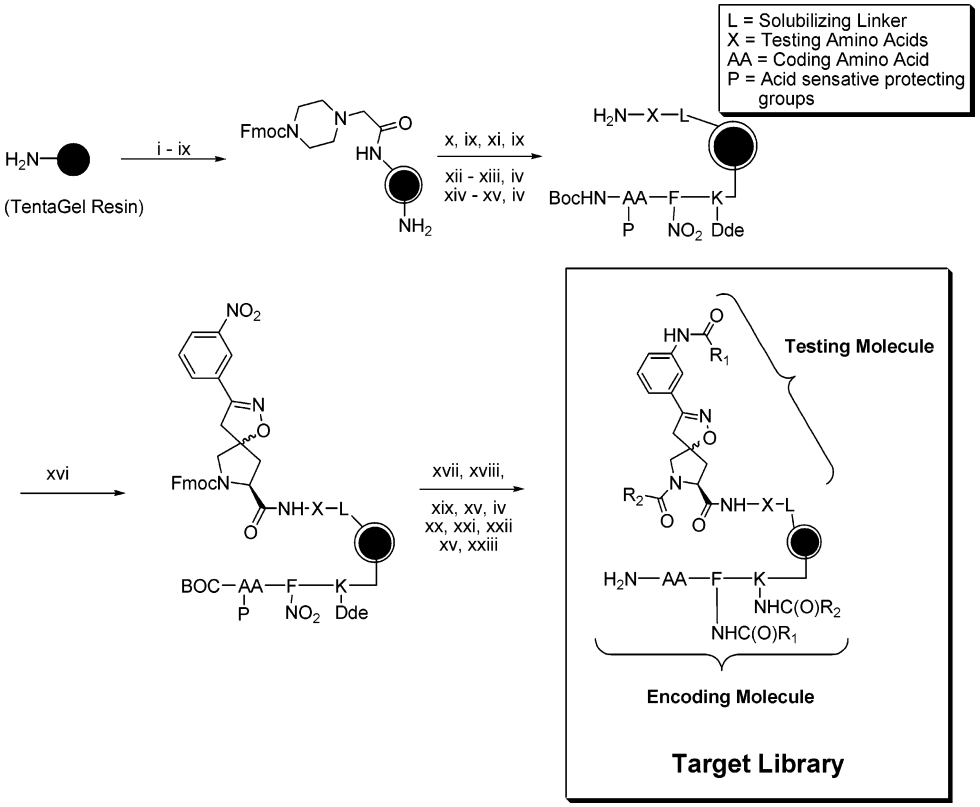


Figure 1. Expanded HPLC traces of (A) **10e(maj)**, the major diastereomer of **10e**, (B) **10e(min)**, the minor diastereomer of **10e**, and (C) **10e**, the mixture of diastereomers.

Scheme 4. Encoded Small Molecule Library Synthesis.[a]



[a] Reagents and conditions: (i) H_2O, 48 h; (ii) Fmoc-OSu (0.1 equiv), DIEA, DCM/Et_2O (55:45, v/v), 30 min; (iii) Boc_2O (1.1 equiv), DIEA, DMF; (iv) 20% piperidine in DMF, 2 × 10 min; (v) 2-bromoacetic acid, HOBt, DIC, DMF; (vi) piperazine, DIEA, DMF, 16 h; (viii) Fmoc-OSu, DIEA, DMF; (ix) TFA/H_2O/TIS (95:2.5:2.5); (x) Boc-Lys(Dde)−OH, HOBt, DIC, DMF; (xi) Boc-Phe(4-NO_2)−OH, HOBt, DIC, DMF; (xii) split resin into 96 columns; (xiii) Boc-AA(P)−OH, HOBt, DIC, DMF; (xiv) Fmoc-X(P)−OH, HOBt, DIC, DMF; (xv) mix resin; (xvi) mixture of **7a** and **b** (4:1), HOBt, DIC, DMF; (xvii) $SnCl_2$·$2H_2O$ (30 equiv), DMF, 2 h; (xviii) split resin into 30 columns; (xix) R_1−CO_2H, HOBt, DIC, DMF; (xx) 2% hydrazine in DMF, 2 × 10 min; (xxi) split resin into 45 columns; (xxii) R_2−CO_2H, HOBt, DIC, DMF; (xxiii) TFA/phenol/TIS/H_2O/EDT (90/5/2/2/1, v/w/v/v/v).

Experimental Section

Reagents and Instrumentation. All reagents and solvents were purchased from commercial suppliers and used without further purification. Fmoc-Rink amide MHBA resin (capacity: 0.50 mmol/g) was purchased from EMD Biosciences (San Diego, CA). TentaGel S NH_2 resin (90 μm, 0.26 mmol/g) was purchased from Rapp Polymere GmbH (Tübingen, Germany), and all the calculations for synthesis were based on a substitution of 0.26 mmol/g. HOBt, Fmoc-OSu, and DIC were purchased from GL Biochem (Shanghai, China). All infrared spectra were determined on a Genesis II Mattson FT−IR. ^{1}H and ^{13}C NMR were measured in either DMSO-d_6 or $CDCl_3$ at 600 (or 400) and 150 (or 100) MHz, respectively. Elemental analyses were determined at MidWest Microlab, Indianapolis, IN. MALDI-TOF-MS analyses were performed with a Bruker Biflex III MALDI-TOF mass spectrometer (Bruker-Franzen Analytik, Bremen, Germany) equipped with a pulsed N_2 laser (337 nm), a delayed extraction ion source, and a reflectron. For HPLC analyses, the following were used: a Waters Alliance LC/MS, a Waters 2695 HPLC, and a Waters PDA 996 equipped with a 2.1 × 50 mm Water Xterra MS C_{18} 3.5-μm column employing a gradient elution of 0−5 min, 100% A; 5−25 min, 0−100% B; 25−30 min, 100−0% B; 30−35 min, 100% A (solvent A, H_2O/0.1% TFA; B, acetonitrile/0.1% TFA) monitored from 200 to 400 nm using a 0.2 mL/min flow rate. A Waters Micromass ZQ Mass detector was used for the identification of MS (ESI) for various products, with product concentration of ∼1 μg/mL. Autopurification preparative HPLC was performed on a Waters 2487 Dual λ Absorbance Detector, a Waters 600 Controller, a Waters 2767 Sample Manager equipped with a 19 × 100 mm Waters Xterra Prep MS C_{18} 5.0-μm OBD column employing a gradient elution of 0−30 min, 0−60% B; 30−40 min, 60−80% B; 40−45 min, 80−100% B; 45−50 min, 100% B; 50−53 min, 100−0% B; 53−60 min, 100% A (solvent A, H_2O/0.1% TFA; B, acetonitrile/0.1% TFA) monitored at 254 nm at a flow rate of 7.0 mL/min. Further preparative HPLC was performed on a System Gold 126NMP Solvent Module (Beckman) with a C_{18} column (Vydac, 5 μM, 2.5-cm i.d. × 25 cm). A gradient elution of 0−60% B over 25 min followed by 60−100% B over 25 min followed by 100% B for 5 min was used at a flow rate of 7 mL/min (solvent A, H_2O/0.1% TFA; B, acetonitrile/0.1% TFA). Edman degradation sequencing was performed on an ABI 494 protein sequencer (Applied Biosystems).

Synthesis of Methyl (2*S*,4*R*)-4-Hydroxypyrrolidine-2-carboxylate Hydrochloride (1). *trans*-4-Hydroxy-L-proline (100 g, 762.6 mmol) was added to a stirring solution of MeOH (150 mL) in a 500-mL flask at 0 °C under N_2. To this solution was added acetyl chloride (71.8 g, 915.1 mmol, 65.1 mL) dropwise via syringe. The solution was stirred at 0 °C for 15 min then refluxed for 8 h, after which the solution was cooled to 0 °C in an ice bath and then was poured into a stirring solution of ice-cold Et_2O. The precipitate was

collected by filtration and dried under vacuum. The product was used without further purification as the HCl salt (117 g, ~100% yield). IR (neat, selected peaks): 3321, 1739, 1591, 1438 cm^{-1}. MS (ESI) *m/z*: 146.23 [M + H^+]. ^1H NMR (400 MHz, DMSO-d_6): δ 5.63 (s, br, 1H), ~4.45 to 4.39 (m, 2H), 3.73 (s, 3H), 3.35 (dd, 1H, J = 12.0, 4.4 Hz), 3.04 (d, 1H, J = 12.4 Hz), ~2.20 to 2.02 (m, 2H). ^{13}C NMR (100 Hz, DMSO-d_6): δ 169.0, 68.4, 57.4, 53.1, 53.0, 37.0.

Synthesis of 1-*tert*-Butyl-2-methyl (2*S*,4*R*)-4-Hydroxypyrrolidine-1,2-dicarboxylate (2). In a 1-L round-bottom flask was placed **1** (117 g, 762.6 mmol) and DCM (150 mL). To this solution was added triethylamine (270.4 g, 2.67 mol, 372.5 mL), and the system was cooled to 0 °C in an ice bath and place under N_2. Di-*tert*-butyl dicarbonate (183.1 g, 838.9 mmol) was dissolved in DCM (100 mL) and added via syringe to the solution, which effervesced vigorously. The solution was allowed to stir overnight, during which time the ice bath expired. The reaction mixture was then washed with 1 M phosphoric acid (100 mL, 3 times) and saturated sodium carbonate (100 mL, 3 times), dried with magnesium sulfate, filtered, and concentrated under rotary evaporation until an off-white solid was formed, which was used without further purification (183 g, 98% yield). IR (neat, selected peaks): 3436, 1737, 1659, 1419 cm^{-1}. HPLC analysis: t_R = 10.70 min, purity = 99.0%. MS (ESI) *m/z*: 246.14 [M + H^+]. ^1H NMR (400 MHz, $CDCl_3$, mixture of conformers): δ ~4.46 to 4.37 (m, 2H), 3.73 (s, 3H), ~3.62 to 3.43 (m, 3H), ~2.33 to 2.28 (m, 1H), ~2.07 to 2.02 (m, 1H), 1.43 (2 s, 9H). ^{13}C NMR (100 Hz, $CDCl_3$, mixture of conformers): δ 173.9, 154.2, 80.5, 80.4, 70.0, 69.2, 58.1 57.7, 54.7, 52.2, 39.1, 38.5, 28.5, 28.3.

Synthesis of 1-*tert*-Butyl-2-methyl (*S*)-4-Oxopyrrolidine-1,2-dicarboxylate (3). Sodium periodate (354 g, 1.66 mol) was placed in a 1-L round-bottom flask containing water (300 mL). To this suspension was added EtOAc (100 mL) and ruthenium(IV) oxide hydrate (99.4 mg, 0.75 mmol). With vigorous stirring, the biphasic reaction mixture changed color from black to yellow and was then placed in an ice bath. A solution of **2** (183 g, 753 mmol) dissolved in EtOAc (100 mL) was added dropwise to the above solution. The ice bath was removed, and vigorous stirring was maintained until the solution had gone to green-black, after which time the TLC had shown the reaction had gone to completion. EtOAc was added, the solution was thoroughly mixed, and the organic and aqueous layers were then allowed to separate. The organic layer was decanted off, and the remaining water layer was extracted with EtOAc (150 mL, 3 times). The organic solutions were combined, isopropyl alcohol was added (30 mL), and the solution was filtered through a pad of Celite. The filtered organic layers were dried with magnesium sulfate, filtered, and concentrated by rotary evaporation to deliver the product as a pale yellow oil that was used without further purification (172 g, 94% yield). IR (neat, selected peaks): 1764, 1747, 1700 cm^{-1}. HPLC analysis: t_R = 11.42 min, purity = 97.8%. MS (ESI) *m/z*: 244.25 [M + H^+]. ^1H NMR (400 MHz, $CDCl_3$, mixture of conformers): δ ~4.82 to 4.71 (m, 1H), 3.89 (m, 2H), 3.77 (s, 3H), ~3.02 to 2.91 (m, 1H), ~2.61 to 2.56 (m, 1H), 1.47 (2 s, 9H). ^{13}C NMR (100 Hz, $CDCl_3$, mixture of conformers): δ 208.4, 207.6, 172.3, 154.3, 153.5, 81.2, 60.3, 56.3, 55.6, 52.8, 52.5, 41.2, 40.7, 28.2.

Synthesis of 1-*tert*-Butyl 2-Methyl (*S*)-4-Methylenepyrrolidine-1,2-dicarboxylate (4). Methyltriphenylphosphonium bromide (505.7 g, 1.42 mol) was placed in a 3-L round-bottom flask, and the flask was put into an ice bath. Potassium *tert*-butoxide (1.49 L of a 1.0 M solution in THF, 1.49 mol) was added to the reaction mixture, which was then allowed to stir at 0 °C for 30 min. The reaction mixture was warmed to room temperature and allowed to stir for 30 min, followed by refluxing for 1 h, after which the reaction mixture was cooled in an ice bath, and **3** (172 g, 707.8 mmol) was added via pipet. The reaction mixture was removed from the ice bath and brought to reflux until TLC showed the reaction to be complete. The reaction mixture was diluted with water, concentrated by rotary evaporation, and extracted with EtOAc (300 mL, 3 times). The organic layers were combined, dried with magnesium sulfate, filtered, and concentrated by rotary evaporation. Purification by flash chromatography (EtOAc/hexane, 1:5) gave the pure final product as a pale yellow oil (107.5 g, 63% yield). IR (neat, selected peaks): 2976, 1748, 1699 cm^{-1}. HPLC analysis: t_R = 12.30 min, purity = 99.9%. MS (ESI) *m/z*: 242.12 [M + H^+]. ^1H NMR (400 MHz, DMSO-d_6, mixture of conformers): δ 5.01 (d, 2H, J = 10.8 Hz), 4.36 (t, 1H, J = 11.2 Hz), 3.95 (2 s, 2H), 3.64 (2 s, 3H), 3.01 (q, 1H, J = 14.6 Hz), ~2.57 to 2.50 (m, 1H), 1.38 (2 s, 9H). ^{13}C NMR (100 Hz, DMSO-d_6, mixture of conformers): δ 172.7, 172.4, 153.5, 152.9, 143.4, 142.5, 107.8, 79.3, 79.2, 58.5, 58.1, 51.9, 50.5, 50.4, 36.0, 35.3, 28.0, 27.8. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81; O, 26.52. Found: C, 59.67; H, 7.91; N, 5.82; O, 26.60.

Synthesis of 3-Nitrobenzaldehyde Oxime (5). 3-Nitrobenzaldehye (10.0 g, 66.2 mmol) was added to a stirring solution of hydroxylamine hydrochloride (9.2 g, 132.3 mmol) in a solution of water, THF, and ethanol (100 mL, 1:5:2) in a 250 mL round-bottom flask. To this solution was added NaOAc (16.3 g, 198.5 mmol), and the reaction mixture was stirred for 1 h, at which time the TLC showed the reaction to be complete. The THF and ethanol were removed by rotary evaporation, and the remaining aqueous layer was extracted with DCM (50 mL, 3 times). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated by rotary evaporation to give the final product (*E* and *Z* isomers) as a yellow powder (10.98 g, 99.8% yield), which was used without further purification. IR (neat, selected peaks): 3323, 1531, 1347 cm^{-1}. HPLC analysis: t_R = 4.47 min, purity = 98.2%. MS (ESI) *m/z*: 167.08 [M + H^+]. ^1H NMR (400 MHz, DMSO-d_6): δ 11.69 (s, 1H), ~8.43 to 8.42 (m, 1H), 8.34 (s, 1H), 8.22 (ddd, 1H, J = 8.4, 2.4, 0.8 Hz), 8.06 (dt, 1H, J = 8.0, 1.2 Hz), 7.71 (t, 1H, J = 8.0 Hz). ^{13}C NMR (100 Hz, DMSO-d_6): δ 148.1, 146.6, 134.9, 132.3, 130.3, 123.7, 120.8.

Synthesis of *N*-Hydroxy-3-nitrobenzimidoyl Chloride (6). In a 1-L round-bottom flask, **5** (10.0 g, 60.2 mmol) was dissolved in $CHCl_3$ (350 mL), and the reaction mixture was placed in an ice bath. Pyridine (0.476 g, 6.02 mmol, 486.8 μL) was added to this system via pipet, and the mixture was allowed to stir for 15 min. After this time, *N*-chlorosuccin-

imide (8.84 g, 66.2 mmol) was dissolved in $CHCl_3$ (100 mL), and the resulting suspension was added to the reaction mixture at 0 °C. The reaction was allowed to stir overnight, after which time the TLC showed the reaction to be complete. The reaction mixture was concentrated, and water and DCM were added. The layers were separated, and the aqueous layer was extracted twice more with DCM. The combined organic layers were dried with magnesium sulfate, filtered, and concentrated by rotary evaporation to produce a yellow oil, which solidified into a yellow solid over time in the refrigerator and was used without further purification (*E* and *Z* isomeric mixture; 11.53 g, 95.5% yield). IR (neat, selected peaks): 3308, 1527, 1352 cm^{-1}. MS (ESI) *m*/*z*: 201.14 [M + H^+]. ^1H NMR (400 MHz, DMSO-d_6): δ 9.49 (2 s, 1H), 8.63 (t, 1H, J = 2.0 Hz), 8.24 (ddd, 1H, J = 8.0, 2.0, 0.8 Hz), 8.13 (dt, 1H, J = 8.0, 1.2 Hz), 7.57 (t, H, J = 8.0 Hz). ^{13}C NMR (100 Hz, DMSO-d_6): δ 148.4, 137.5, 134.5, 132.8, 129.8, 125.2, 122.2.

Synthesis of (5*R*,8*S*)-3-(3-Nitrophenyl)-1-oxa-2,7-diazaspiro[4,4]-non-2-ene-7-*N*-Fmoc-8-carboxylic Acid and (5*S*,8*S*)-3-(3-Nitrophenyl)-1-oxa-2,7-diazaspiro[4,4]-non-2-ene-7-*N*-Fmoc-8-carboxylic Acid (7). Compounds **4** (107.5 g, 446.1 mmol) and **6** (178.9 g, 892.1 mmol) were dissolved in DCM (350 mL) in a 1-L round-bottom flask, and the reaction mixture was cooled to 0 °C and placed under nitrogen. Triethylamine (112.8 g, 1.12 mol, 155.4 mL) was added to the reaction mixture via syringe. The reaction mixture was vigorously stirred until LC/MS showed the reaction to be complete (~4 h). The reaction mixture was concentrated by rotary evaporation, and water and DCM were added. The aqueous layer was extracted with DCM (150 mL, 2 times), and the organic layers were combined, dried with magnesium sulfate, filtered, and concentrated. The crude mixture was then dissolved in THF (150 mL) and water (150 mL), lithium hydroxide (74.9 g, 1.78 mol) was added to this solution, and the reaction was stirred until TLC showed the reaction to be complete (~6 h), after which the THF was removed by rotary evaporation, and the remaining aqueous layer was extracted with ether (100 mL, 2 times). The reaction mixture was then adjusted to a pH of 2−3 with 1 N HCl, and the aqueous layer was extracted with EtOAc (150 mL, 3 times). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated. This crude mixture was dissolved in trifluoroacetic acid (250 mL), and the solution immediately effervesced vigorously. When TLC showed the reaction's completion, the trifluoroacetic acid was removed by rotary evaporation. Ether (200 mL) was added, and precipitation occurred. The ether and any remaining trifluoroacetic acid were removed by rotary evaporation. This process was repeated 3 more times. The final crude mixture was then dissolved in dioxane (250 mL) and water (100 mL) in a 1-L round-bottom flask, and sodium carbonate was added until the pH reached 7−8. Once this pH was attained, a solution of Fmoc-Osu (180.5 g, 535.3 mmol) dissolved in dioxane (150 mL) was added dropwise over 90 min. The pH was maintained by adding additional sodium carbonate. When the TLC showed the reaction to be complete, the dioxane was removed, and the aqueous layer was extracted with ether (250 mL, 2 times). The aqueous layer was then adjusted to a pH of 2−3 with 1 N HCl and extracted with EtOAc (200 mL, 3 times), and the organic layers were combined, dried with magnesium sulfate, filtered, and concentrated. The resulting crude mixture was subjected to flash chromatography (EtOAc/hexane, 2:1, with 2% acetic acid), and the combined fractions were concentrated and diluted with enough EtOAc such that the addition of this solution to ice-cold hexane resulted in a pale yellow powder that was filtered and dried under vacuum (**7a** and **7b**, 123.6 g, 54% yield). **7a** (major diastereomer). IR (neat): 3066, 3018, 2958, 2936, 2366, 2326, 1782, 1739, 1702, 1681, 1619, 1600, 1531, 1471, 1426, 1348 cm^{-1}. HPLC analysis: t_R = 22.10 min, purity = 99.9%. MS (ESI) *m*/*z*: 514.16 [M + H^+]. ^1H NMR (400 MHz, DMSO-d_6, mixture of conformers): δ 8.39 (s, 1H), 8.33 (d, 2H, J = 7.6 Hz), 8.10 (t, 1H, J = 6.8 Hz), 7.90 (dd, 1H, J = 6.8, 3.2 Hz), ~7.81 to 7.76 (m, 1H), ~7.71 to 7.67 (m, 2H), 7.43 (q, 2H, J = 7.2 Hz), 7.35 (q, 2H, J = 7.2 Hz), 4.53 (t, 1H, J = 8.4 Hz), ~4.40 to 4.19 (m, 3H), 3.88 (d, 1H, J = 11.6 Hz), ~3.78 to 3.55 (m, 1H), ~2.83 to 2.67 (m, 2H), ~2.41 to 2.26 (m, 2H). ^{13}C NMR (100 Hz, DMSO-d_6, mixture of conformers): δ 173.3, 172.8, 156.2, 156.1, 153.9, 153.8, 148.0, 143.8, 143.7, 143.7, 143.6, 140.8, 140.7, 140.6, 132.7, 130.9, 130.6, 127.8, 127.2, 125.3, 125.3, 125.1, 124.7, 124.1, 121.0, 120.2, 91.5, 90.7, 67.4, 67.0, 58.3, 57.9, 56.7, 56.2, 46.6, 46.5, 41.1. HRMS (MALDI-TOF, [M + Na^+]): calcd, 536.1434; found, 536.1433. Anal. Calcd for $C_{28}H_{23}N_3O_7$: C, 65.49; H, 4.51; N, 8.18; O, 21.81. Found: C, 65.54; H, 4.59; N, 7.96, O, 21.91.

7b. Minor diastereomer. IR (neat): 3066, 3018, 2958, 2936, 2366, 2326, 1782, 1739, 1702, 1681, 1619, 1600, 1531, 1471, 1426, 1348 cm^{-1}. HPLC analysis: t_R = 21.70 min, purity = 99.9%. MS (ESI) *m*/*z*: 514.16 [M + H^+]. ^1H NMR (400 MHz, DMSO-d_6, mixture of conformers): δ 8.40 (s, 1H), 8.33 (d, 2H, J = 7.6 Hz), 8.10 (t, 1H, J = 6.8 Hz), 7.90 (dd, 1H, J = 6.8, 3.2 Hz), ~7.82 to 7.76 (m, 1H), ~7.71 to 7.66 (m, 2H), 7.42 (q, 2H, J = 7.2 Hz), 7.34 (q, 2H, J = 7.2 Hz), 4.55 (d, 1H, J = 8.4 Hz), ~4.44 to 4.19 (m, 3H), ~3.77 to 3.60 (m, 2H), ~2.67 to 2.55 (m, 2H), ~2.45 to 2.35 (m, 2H). ^{13}C NMR (100 Hz, DMSO-d_6, mixture of conformers): δ 172.4, 172.0, 157.9, 155.8, 153.7, 147.9, 143.7, 143.6, 140.6, 132.6, 130.8, 130.5, 127.6, 127.1, 125.2, 125.1, 124.5, 123.9, 120.9, 120.1, 91.4, 90.5, 66.9, 66.8, 58.1, 57.9, 56.5, 55.9, 46.6, 46.5, 41.2, 41.0. HRMS (MALDI-TOF, [M + Na^+]): calcd, 536.1434; found, 536.1436. Anal. Calcd for $C_{28}H_{23}N_3O_7$: C, 65.49; H, 4.51; N, 8.18; O, 21.81. Found: C, 65.45; H, 4.61; N, 8.21, O, 21.73.

Synthesis of 3-(3-Phenyl-4,5-dihydroisoxazol-5-yl)propanoic Acid (8). 4-Pentenoic acid (10.0 g, 99.9 mmol) and benzaldehyde oxime (24.2 g, 299.8 mmol) were dissolved in THF (50 mL) in a 1-L round-bottom flask, and the reaction mixture was cooled in an ice bath to 0 °C. Aqueous sodium hypochlorite (29.7 g, 475.8 mL of a 6.25% bleach solution, 399.5 mmol) was added dropwise via a dropping funnel over 120 min, and the resulting solution was stirred vigorously overnight, during which time the ice bath expired. After this time, TLC showed the reaction to be complete, and the THF was removed by rotary evaporation. The remaining aqueous layer was extracted with EtOAc (100 mL, 3 times). The

organic layers were combined, dried with magnesium sulfate, filtered, and concentrated. The crude mixture was purified by flash chromatography (EtOAc/hexane, 1:2, with 1% acetic acid) to deliver the final product as an off-white powder (18.8 g, 86% yield). IR (neat): 3025, 2969, 2920, 2779, 2694, 2656, 2578, 1702, 1598, 1568, 1497, 1434, 1412, 1352 cm^{-1}. HPLC analysis: $t_R = 15.73$ min, purity = 98.7%. MS (ESI) *m/z*: 219.06 [M^+]. ^1H NMR (400 MHz, DMSO-d_6): δ 12.19 (s, 1H), ~7.68 to 7.65 (m, 2H), ~7.47 to 7.45 (m, 3H), ~4.75 to 4.67 (m, 1H), ~3.52 to 3.45 (m, 1H), ~3.15 to 3.09 (m, 1H), 2.36 (t, 2H, $J = 7.6$ Hz), 1.84 (q, 2H, $J = 7.2$ Hz). ^{13}C NMR (100 Hz, DMSO-d_6): δ 174.0, 156.7, 130.0, 129.6, 128.8, 126.6, 79.9, 29.9, 29.7. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 65.74; H, 5.98; N, 6.39; O, 21.89. Found: C, 65.70; H, 5.99; N, 6.36; O, 21.95.

Synthesis of 3-(3-(3-Nitrophenyl)-4,5-dihydroisoxazol-5-yl)propanoic Acid (9). The preparation of **8** was modified as follows to deliver **9**: 3-Nitrobenzaldehyde oxime (33.2 g, 199.8 mmol), aqueous sodium hypochlorite (29.7 g, 475.8 mL of a 6.25% bleach solution, 399.5 mmol), and flash chromatography (EtOAc/hexane, 1:2, with 1% acetic acid) delivered **9** as a yellow powder (24.3 g, 92% yield). IR (neat): 3107, 3077, 2943, 2928, 2869, 1725, 1691, 1598, 1531, 1486, 1438, 1415, 1348 cm^{-1}. HPLC analysis: $t_R =$ 16.28 min, purity = 99.2%. MS (ESI) *m/z*: 264.08 [M^+]. ^1H NMR (400 MHz, DMSO-d_6): δ 12.21 (s, 1H), 8.39 (s, 1H), 8.29 (d, 1H, $J = 8.0$ Hz), 8.10 (d, 1H, $J = 7.2$ Hz), 7.76 (t, 1H, $J = 8.0$ Hz), ~4.86 to 4.78 (m, 1H), ~3.61 to 3.54 (m, 1H), ~3.27 to 3.21 (m, 1H), 2.38 (t, 2H, $J = 8.0$ Hz), 1.88 (q, 2H, $J = 7.2$ Hz). ^{13}C NMR (100 Hz, DMSO-d_6): δ 174.6, 156.3, 148.6, 133.3, 131.8, 131.1, 125.0, 121.5, 81.5, 39.4, 30.5, 30.2. Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58; N, 10.60; O, 30.28. Found: C, 54.43; H, 4.56; N, 10.51, O, 30.50.

General Procedures for Solid-Phase Arylnitro Reduction Studies. Fmoc-Rink MHBA amide resin (50.0 mg, 0.5 mmol/g loading capacity) was placed in a disposable plastic column and swollen in DMF for 2 h, after which a solution of 20% piperidine in DMF was added to the resin, and the column was rotated for 5 min. At the end of this time, the column was drained and washed two times with DMF, then 20% piperidine in DMF was added, and the column was rotated for 15 min. After this deprotection, compounds **8** and **9** (3.0 equiv) were individually added to columns containing Rink resin along with HOBt and DIC (3.5 equiv each) in DMF. The reaction was allowed to proceed until the Kaiser test indicated completion. The resin was washed with DMF (3 times); water (3 times); MeOH (3 times); DCM (5 times); and finally, DMF (2 times). Tin(II) chloride dihydrate was dissolved in DMF and added in varying amounts to the columns. The reaction was allowed to proceed for 2 h at room temperature, at which time the solution was drained, and the resin was washed with water (5 times), MeOH (5 times), and DCM (7 times). Once the resin was thoroughly washed, a solution of TFA, water, and TIS (95:2.5:2.5, v/v/v) was added, and the cleavage reaction was allowed to react with the resin for 2 h, after which time the cleavage solution was collected, and the resin was washed with TFA and then DCM. The volatile solvents were removed under a constant stream of air, and the crude mixture was taken without further purification and analyzed by LC/MS.

General Procedure for the Synthesis of Compounds 10a−10t. Fmoc-Rink MHBA amide resin (500 mg, 0.5 mmol/g) was placed in a disposable plastic column and swollen in DMF for 2 h, after which a solution of 20% piperidine in DMF was added to the resin, and the column was rotated for 5 min. At the end of this time, the column was drained and washed with DMF (2 times), then 20% piperidine in DMF was added, and the column was rotated for 15 min. Once the deprotection was complete, the appropriate Fmoc-L-amino acid (3.0 equiv) was dissolved in DMF along with HOBt (3.5 equiv) and DIC (3.5 equiv) and was added to this reaction mixture. When the Kaiser test indicated reaction completion, the solution was drained, and the resin was washed with DMF (2 times); water (3 times); MeOH (3 times); DCM (5 times); and finally, DMF (2 times). The Fmoc deprotection procedure outlined above was repeated, and compounds **7a** and **7b** (4:1) were coupled to the N terminus according to the procedure outlined above for the amino acid. The reaction was monitored by the Kaiser test. Once complete, the resin was drained and washed as outlined above. Tin(II) dichloride dihydrate (30.0 equiv) dissolved in DMF was added to the resin, and the reaction was allowed to proceed for 2 h. The resin was then drained and washed, and the appropriate carboxylic acid (R_1) was coupled to the amino group of the aniline with HOBt and DIC. When a modified chloranil test[35] showed the reaction to be complete, the resin was drained and washed and subjected to Fmoc deprotection. The resin was washed, and the appropriate carboxylic acid (R_2) was coupled to the secondary amine with HOBt and DIC in DMF as outlined above. When the standard chloranil test indicated the reaction had gone to complete, the resin was thoroughly washed with water (5 times), MeOH (5 times), and DCM (7 times), and a solution of TFA, water, and TIS (95:2.5:2.5, v/v/v) was added if the target compound did not contain sulfur. If the target compound did contain a sulfur, then a solution of TFA, phenol, TIS, water, and EDT (90:5:2:2:1, v/w/v/v/v) was added to the resin. Once the cleavage reaction had run for 2 h, the solution was drained and collected. The resin was washed with TFA and DCM, which was also collected. The volatile liquids were removed under a constant stream of air, and when dry, ether was added. Precipitation occurred immediately. The precipitation was allowed to develop in the refrigerator overnight, and then the solution was centrifuged. The ether was decanted, the crude material was brought into solution with DCM, and the whole process was repeated three times. When the final decantation was complete, the crude solid was dried under vacuum for 24 h. The crude solid was dissolved and purified by HPLC, and upon drying, each compound was analyzed.

10a. Crude yield, 116 mg, 83%; crude purity, 91%. HPLC-purified ~4:1 mixture of diastereomers: purity = 99.18%; $t_R = 18.44$ min; LRMS (ESI, [M + H^+]) = 679.15. IR (neat): 3318, 3276, 2364, 2316, 1671, 1614, 1576, 1574, 1500, 1424 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6, mixture of diastereomers): δ 10.24 and 10.24 (s, 0.2H and 0.8H), 8.35 and 8.27 (d, 1H, $J = 8.4$ Hz), ~7.91 to 8.0 (m, 2H),

7.84 (d, 1H, $J = 8.4$ Hz), 7.75 and 7.71 (d, 0.4H and 1.6 H, $J = 8.4$ Hz), ~7.59 to 7.05 (m, 12H), 4.67 (t, 1H, $J = 8.7$ Hz), 4.61 and 4.36 (q, 0.2H and 0.8H, $J = 8.7$ Hz), ~4.22 to 4.18 (m, 1H), 4.03 (d, 1H, $J = 13.2$ Hz), 3.91 (d, 1H, $J = 12$ Hz), 3.77 and 3.73 (d, 0.2H and 0.8H, $J = 11.7$ Hz), ~3.12 to 3.63 (m, 4H), 2.88 (q, 1H, $J = 7.2$ Hz), ~2.58 to 2.61 (m, 2H), ~1.96 to 2.48 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, mixture of diastereomers): δ 177.5, 172.6, 171.6, 170.6, 169.1, 157.1, 139.5, 139.2 (2 carbons), 139.0, 135.5, 132.4, 130.6, 129.9 (2 carbons), 129.7, 129.5, 128.4, 127.6, 124.1, 123.7, 121.9, 121.0, 116.9, 116.5, 90.6, 59.6, 56.5, 54.8, 52.5, 32.1, 30.5, 30.3, 30.0, 29.2, 25.3. HRMS (MALDI-TOF, [M + Na^+]): calcd, 701.2158; found, 701.2154.

10b. Crude yield, 139 mg, 92%; crude purity, 93%. HPLC-purified ~4:1 mixture of diastereomers: purity = 99.29%, t_R = 19.18 min; LRMS (ESI, [M + H^+]): 737.21. IR (neat): 3318, 3276, 2359, 2212, 1671, 1619, 1566, 1552, 1486, 1429 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, mixture of diastereomers): δ 10.19 (s, 1H), ~8.69 to 8.75 (m, 1H), 8.62 and 8.54 (d, 0.8H and 0.2 H, $J = 8.4$ Hz), 8.40 and 8.36 (d, 0.8H and 0.2H, $J = 8.4$ Hz), 8.28 and 8.12 (d, 1.6H and 0.4H, $J = 8.4$ Hz), ~8.00 to 7.87 (m, 2H), ~7.74 to 7.71 (m, 2H), ~7.63 to 7.18 (m, 9H), 6.70 (d, 0.2H, $J = 9.6$ Hz), 6.33 (d, 0.8H, $J = 15$ Hz), 5.53 and 5.46 (d, 0.2H and 0.8H, 9.6 Hz), ~4.66 to 4.35 (m, 2H), 4.20 (dd, 1H, $J = 4.2$ Hz), ~3.99 to 3.68 (m, 1H), ~3.60 to 2.73 (m, 4H), ~2.64 to 1.78 (m, 6H), 1.20 (d, 1H, $J = 6.0$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): δ 177.5, 172.7, 171.6, 170.6, 163.1, 156.9, 139.5, 139.2 (2 carbons), 138.9, 138.7, 132.6, 132.0, 131.5, 131.4, 131.3, 131.2, 130.5, 129.9 (2 carbons), 129.8, 129.6, 129.5, 129.4, 128.7, 124.2, 124.1, 123.6, 122.9, 121.9, 121.0, 116.9, 90.3, 59.6, 56.4, 52.4, 29.2, 25.3. HRMS (MALDI-TOF, [M + Na^+]): calcd, 759.2035; found, 759.2038.

10c. Crude yield, 143 mg, 85%; crude purity, 84%. HPLC-purified ~4:1 mixture of diastereomers: purity = 99.44%, t_R = 20.58 min; LRMS (ESI, [M + H^+]): 813.19. IR (neat): 3456, 3342, 3285, 2359, 2321, 1676, 1609, 1576, 1552, 1528, 1467, 1424 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, mixture of diastereomers): δ 10.24 and 10.22 (s, 0.2H and 0.8H), 8.76 (d, 1H, J = 5.6 Hz), 8.67 (d, 1H, $J = 5.6$ Hz), 8.43 (d, 1H, $J = 8.4$ Hz), ~8.03 to 7.71 (m, 8H), ~7.61 to 7.50 (m, 4H), ~7.44 to 7.26 (m, 6H), 5.26 (t, 1H, $J = 7.8$ Hz), ~4.67 to 4.50 (m, 2H), ~4.37 to 1.84 (m, 8H), ~1.23 to 1.17 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6, mixture of diastereomers): δ 177.5, 172.6, 171.6, 170.3, 159.3, 159.1, 157.6, 157.3, 157.0, 156.6, 155.6, 139.5, 139.2, 138.9, 134.8, 133.9, 133.8, 132.4, 131.9, 130.8, 130.7, 130.3, 130.1, 129.7, 128.2, 127.8, 127.7, 126.6, 126.5, 126.0, 124.1, 122.8, 121.9, 120.6, 119.8, 116.9, 90.8, 56.5, 29.2, 25.3. HRMS (MALDI-TOF, [M + Na^+]): calcd, 835.1484; found, 835.1486.

10d. Crude yield, 141 mg, 91%; crude purity, 88%. HPLC-purified ~4:1 mixture of diastereomers: purity = 96.07%, t_R = 19.29 min; LRMS (ESI, [M + H^+]): 757.31. IR (neat): 3279, 3085, 2928, 2366, 2325, 1669, 1650, 1605, 1557, 1449, 1415 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, mixture of diastereomers): δ 10.23 (s, 1H), 8.75 (d, 1H, $J = 9.0$ Hz), 8.39 (d, 1H, $J = 8.4$ Hz), ~8.01 to 6.97 (m, 15H), 6.79 (d, 1H, 15.6 Hz), 4.83 (t, 1H, $J = 7.8$ Hz), ~4.58 to 4.50 (m, 1H), 4.20 (dd, 1H, $J = 4.4$ Hz), ~4.10 to 3.73 (m, 2H), 3.65 to 3.00 (m, 4H), ~2.46 to 2.12 (m, 2H), ~2.08 to 1.76 (m, 3H), 1.19 (d, 1H, $J = 6.0$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): δ 177.5, 172.9, 172.7, 171.6, 170.5, 164.1, 162.3, 159.8, 157.0, 139.5, 139.2, 138.9, 138.7, 132.6, 132.5, 132.4, 129.8, 129.7, 129.4, 126.2, 124.2, 124.1, 124.0, 123.7, 122.9, 121.9, 121.0, 116.9, 115.6, 115.4, 90.4, 89.2, 59.8, 58.7, 56.4, 52.5, 29.2, 25.3. HRMS (MALDI-TOF, [M + Na^+]): calcd, 779.1831; found, 779.1834.

10e. Crude yield, 135 mg, 89%; crude purity, 91%. HPLC-purified ~4:1 mixture of diastereomers: purity = 99.60%, t_R = 19.12 min; LRMS (ESI, [M + H^+]): 739.31. IR (neat): 3318, 3276, 3209, 2359, 2321, 1671, 1604, 1600, 1547, 1500, 1424 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, mixture of diastereomers): δ 10.24 and 10.22 (s, 0.2H and 0.8H), 8.78 (d, 0.2H, $J = 8.4$ Hz), 8.36 (d, 0.8H, $J = 8.4$ Hz), ~7.98 to 7.93 (m, 4H), ~7.56 to 7.07 (m, 12H), ~4.75 to 4.45 (m, 2H), ~4.22 to 4.20 (dd, 1H, $J = 3.6$ Hz), ~4.05 to 3.32 (m, 6H), ~3.23 to 2.87 (m, 4H), ~2.61 to 1.95 (m, 4H), 1.26 and 1.15 (t, 2.4H and 0.6H, $J = 7.8$ Hz). ^{13}C NMR (150 MHz, DMSO-d_6, mixture of diastereomers): δ 177.6, 172.7, 171.6, 170.6, 168.7, 158.6, 158.3, 157.1, 140.3, 139.6, 139.5, 139.2 (2 carbons), 139.0, 138.7, 132.4 (2 carbons), 131.8, 129.7, 129.4, 128.6, 126.3, 124.1, 123.8, 123.7, 122.9, 122.0, 121.1, 117.0, 90.7, 90.6, 59.9, 56.5, 56.4, 52.5, 29.3, 25.3, 14.2. HRMS (MALDI-TOF, [M + Na^+]): calcd, 761.2192; found, 761.2194.

10e(maj). Pure diastereomer. LC/MS analysis: purity, 99.89%; t_R = 19.46 min; LRMS (ESI, [M + H^+]): 739.21. IR (neat): 3320, 3263, 3207, 2362, 2325, 1668, 1612, 1597, 1549, 1426 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, mixture of conformers): δ 10.18 (s, 1H), 8.31 (d, 1H, $J = 6.8$ Hz), ~7.98 to 7.89 (m, 4H), ~7.54 to 7.20 (m, 12H), ~4.66 to 4.59 (m, 2H), ~4.19 to 4.17 (m, 1H), ~4.03 to 3.34 (m, 6H), ~3.22 to 3.02 (m, 4H), ~2.34 to 2.00 (m, 4H), ~1.40 to 1.15 (m, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, mixture of conformers): δ 177.3, 172.4, 171.5, 170.4, 169.9, 160.6, 158.2, 156.9, 140.0, 139.3 (2 carbons), 139.0, 138.6, 132.3 (2 carbons), 131.7, 129.4, 129.2, 128.3, 126.2, 124.1, 123.9, 123.6, 122.7, 121.9, 121.7, 116.8, 90.5, 59.6, 56.3, 56.2, 52.3, 29.1, 25.2, 13.9. HRMS (MALDI-TOF, [M + Na^+]): calcd, 761.2192; found, 761.2199.

10e(min). Pure diastereomer. LC/MS analysis, purity = 99.92%; t_R = 19.18 min; LRMS (ESI, [M + H^+]): 739.28. IR (neat): 3319, 3275, 3202, 2361, 2325, 1669, 1598, 1549, 1426 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, mixture of conformers): δ 10.18 (s, 1H), 8.72 (d, 1H, $J = 8.4$ Hz), ~7.95 to 7.88 (m, 4H), ~7.50 to 7.19 (m, 12H), ~4.62 to 4.51 (m, 2H), ~4.20 to 4.17 (m, 1H), ~3.96 to 3.03 (m, 10H), ~2.4 to 1.92 (m, 4H), ~1.40 to 1.24 (m, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, mixture of conformers): δ 178.1, 173.5, 171.4, 169.4, 168.8, 157.7, 156.2, 139.8, 139.3 (2 carbons), 138.8, 138.6, 133.1 (2 carbons), 130.3, 129.1, 129.0, 128.8, 127.1, 126.2, 124.9, 123.7, 123.5, 122.4, 117.6, 115.8, 91.3, 60.1, 57.1, 52.9, 30.8, 29.9, 14.6. HRMS (MALDI-TOF, [M + Na^+]): calcd, 761.2192; found,-761.2196.

10f. Crude yield, 134 mg, 86%; crude purity, 94%. HPLC-purified ~4:1 mixture of diastereomers: purity = 97.7%, t_R = 21.45 min; LRMS (ESI, [M + H$^+$]): 762.19. IR (neat): 3456, 3333, 3100, 2355, 2321, 1671, 1623, 1614, 1576, 1543, 1448, 1429, 1348 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, mixture of diastereomers): δ 11.00 and 10.96 (s, 0.2H and 0.8H), ~9.21 to 9.17 (m, 2H), ~9.00 to 8.99 (m, 1H), 8.35 and 8.27 (d, 1H, J = 8.4 Hz), ~8.15 to 8.06 (m, 2H), ~7.98 to 7.83 (m, 5H), ~7.64 to 7.02 (m, 9H), ~4.69 to 4.49 (m, 2H), 4.47 (t, 1H, J = 7.2 Hz), ~4.06 to 3.04 (m, 3H), 2.89 (s, 1H), 2.73 (s, 1H), ~2.37 to 1.76 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, mixture of diastereomers): δ 172.5, 170.5, 169.0, 168.6, 162.2, 161.9, 161.4, 160.2, 158.6, 158.4, 158.3, 158.2, 158.1, 157.4, 157.0, 148.1 (2 carbons), 139.4, 138.9, 138.6, 137.1, 135.4, 132.3, 129.7, 129.3 (2 carbons), 128.0 (4 carbons), 127.5, 122.8, 121.2, 118.1, 90.6, 59.5, 52.3, 29.9. HRMS (MALDI-TOF, [M + Na$^+$]): calcd, 784.1802; found,784.1803.

10g. Crude yield, 138 mg, 82%; crude purity, 84%. HPLC-purified ~4:1 mixture of diastereomers: purity = 95.25%, t_R = 21.49 min; LRMS (ESI, [M + H$^+$]): 820.28. IR (neat): 3328, 3280, 3100, 2929, 2321, 1666, 1628, 1576, 1543, 1429, 1348 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of diastereomers): δ 10.99 (s, 1H), 9.19 (s, 2H), 9.01 (s, 1H), 8.65 (dd, 1H, J = 8.8), ~8.24 to 7.86 (m, 8H), ~7.71 to 6.97 (m, 9H), 6.35 (d, 1H, J = 14.4 Hz), ~4.71 to 4.35 (m, 2H), ~3.99 to 3.13 (m, 4H), ~3.04 to 2.73 (m, 2H), ~2.45 to 1.76 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): δ 172.6, 170.5, 169.3, 162.2, 161.4, 156.8, 148.0 (2 carbons), 139.5, 139.4, 138.8, 138.6 (2 carbons), 137.1 (2 carbons), 132.4, 129.6, 129.3, 128.0 (2 carbons), 124.1, 124.0, 123.5, 123.0, 122.8, 122.2, 121.7, 121.5, 121.2, 118.2, 118.0, 90.6, 90.4, 89.1, 59.3, 56.5, 52.3, 47.6, 37.7, 29.7. HRMS (MALDI-TOF, [M + Na$^+$]): calcd, 842.1679; found, 842.1675.

10h. Crude yield, 103 mg, 56%; crude purity, 84%. HPLC-purified ~4:1 mixture of diastereomers: purity = 96.21%, t_R = 23.84 min; LRMS (ESI, [M + H$^+$]): 896.59. IR (neat): 3428, 3356, 3261, 3209, 3090, 2929, 2359, 2326, 2165, 1671, 1614, 1581, 1543, 1495, 1467, 1424, 1391, 1348 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of diastereomers): Very rough interpretation. Please see main text for details. δ 11.00 (m, 1H), 9.20 (m, 2H), 9.02 (s, 1H), ~8.78 to 7.08 (m, 13H), ~4.67 to 4.05 (m, 2H), ~3.78 to 1.24 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): No data available. Please see main text for details. HRMS (MALDI-TOF, [M + Na$^+$]): calcd, 918.1128; found, 918.1123.

10i. Crude yield, 150 mg, 87%; crude purity, 90%. HPLC-purified ~4:1 mixture of diastereomers: purity = 95.98%, t_R = 22.43 min; LRMS (ESI, [M + H$^+$]): 840.35. IR (neat): 3432, 3337, 3209, 3095, 2359, 2207, 2169, 1657, 1600, 1543, 1410, 1348 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, mixture of diastereomers): δ 10.98 (s, 1H), 9.19 (s, br, 1H), 9.00 (s, 1H), 8.77 (d, 1H, J = 5.6 Hz), ~8.60 to 8.24 (m, 2H), 8.15 (t, 1H, J = 12.6 Hz), ~7.99 to 6.99 (m, 12H), ~6.81 to 6.64 (m, 2H), ~4.87 to 4.49 (m, 2H), ~4.128 to 3.90 (m, 1H), ~3.69 to 3.33 (m, 2H), ~3.21 to 3.01 (m, 1H), 2.89 (s, 1H), 2.73 (s, 1H), ~2.57 to 2.47 (m, 1H), ~1.98 to 1.89 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6, mixture of diastereomers): δ 173.4, 171.2, 164.8, 162.1, 157.7, 148.8 (2 carbons), 140.2, 139.6, 139.4, 137.8, 133.0, 130.5, 130.4, 128.7 (2 carbons), 126.9, 124.9, 124.4, 124.3, 123.6, 122.9, 122.5, 122.3, 122.0, 119.0, 118.8 (2 carbons), 117.5, 116.1, 91.2, 60.5, 57.6, 57.4, 57.3, 53.2, 53.0, 42.9, 36.4, 30.5. HRMS (MALDI-TOF, [M + Na$^+$]): calcd, 862, 1474; found, 862.1475.

10j. Crude yield, 140 mg, 83%; crude purity, 84%. HPLC-purified ~4:1 mixture of diastereomers: purity = 97.65%, t_R = 22.46 min; LRMS (ESI, [M + H$^+$]): 822.46. IR (neat): 3409, 3352, 3314, 3100, 2972, 2929, 2359, 2321, 2169, 1671, 1614, 1600, 1538, 1495, 1424, 1348 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of diastereomers): δ 11.0 and 10.96 (s, 0.2H and 0.8H), 9.18 (s, 2H), 9.00, (s, 1H), 8.76 (d, 1H, J = 8.8 Hz), 8.35 (d, 1H, J = 8 Hz), ~8.15 to 7.84 (m, 4H), ~7.56 to 7.18 (m, 8H), ~4.75 to 4.44 (m, 2H), ~4.07 to 3.35 (m, 4H), ~3.07 to 3.00 (m, 2H), 2.82 (s, 1H), 2.73 (s, 1H), 2.51 (s, 1H), 2.38 to 1.77 (m, 3H), 1.26 (t, 3H, J = 6.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): δ 172.6, 170.5, 168.7, 168.2, 162.3, 161.4, 158.5, 158.1, 157.3, 148.1 (2 carbons), 140.2, 139.5, 139.0, 138.7, 137.1, 132.4, 131.8, 129.7, 129.4, 128.5, 128.1 (2 carbons), 126.3 (2 carbons), 124.2, 124.1, 122.9, 122.3, 121.9, 121.2, 118.1, 90.7, 59.8, 52.4, 42.7, 35.8, 30.0, 25.3, 14.0. HRMS (MALDI-TOF, [M + Na$^+$]): calcd, 844.1835; found, 844.1835.

10k. Crude yield, 99 mg, 85%; crude purity, 98%. HPLC-purified ~4:1 mixture of diastereomers: purity = 96.56%, t_R = 15.32 min; LRMS (ESI, [M + H$^+$]): 559.14. IR (neat): 3420, 3301, 3271, 3096, 3059, 2336, 2217, 2198, 2168, 1665, 1613, 1579, 1542, 1497, 1427, 1415, 1367, 1345, 1304 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of diastereomers): δ 10.25 and 10.21 (s, 0.2H and 0.8H), 9.05 (s, 1H), 7.93 (d, 2H, J = 14 Hz), ~7.72 to 7.13 (m, 9H), ~4.54 to 4.50 (m, 1H), ~4.20 to 4.17 (m, 1H), 4.05 (d, 1H, J = 12 Hz), 3.64 (d, 1H, J = 11.6 Hz), 3.51 (q, 1H, J = 17.8 Hz), 2.90 (s, 1H), 2.74 (s, 1H), ~2.39 to 1.97 (m, 6H), ~1.34 to 1.21 (m, 2H), 0.88 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): δ 177.4, 173.5, 171.7, 171.5, 168.9, 157.0, 139.0, 135.1, 130.5, 129.5, 129.2, 128.3 (2 carbons), 128.0, 127.6, 127.3 (2 carbons), 121.8, 120.9, 116.8, 90.6, 60.4, 59.3, 56.3, 33.5, 29.1, 25.2, 15.9, 15.3. HRMS (MALDI-TOF, [M + Na$^+$]): calcd, 581.2125; found, 581.2121.

10l. Crude yield, 107 mg, 84%; crude purity, 96%. HPLC-purified ~4:1 mixture of diastereomers: purity = 95.64%, t_R = 16.70 min; LRMS (ESI, [M + H$^+$]): 617.34. IR (neat): 3472, 3349, 3271, 3197, 2966, 2940, 2876, 2354, 2340, 2321, 1691,1672, 1602, 1572, 1520, 1430, 1412, 1389, 1359, 1311, 1255, 1195, 1177 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of diastereomers): δ 10.29 and 10.22 (s, 0.8H and 0.2H), 9.01 (s, 1H), 7.91 (s, 2H), 7.71 (d, 2H, J = 8.4 Hz), 7.58 (d, 2H, J = 8.8 Hz), ~7.42 to 7.37 (m, 1H), 7.21 (d, 2H, J = 9.6 Hz), 7.00 (d, 2H, J = 8.4 Hz), ~4.52 to 4.48 (m, 1H), ~4.22 to 4.19 (m, 1H), ~4.09 to 3.95 (m, 2H), ~3.69 to 3.44 (m, 2H), ~2.46 to 1.96 (m, 8H), ~1.78 to 1.69 (m, 2H), ~1.33 to 1.20 (m, 2H), 0.97 (t, 3H, J = 7.2 Hz), 0.87 (s, 2H). ^{13}C NMR (100 MHz, DMSO-

d_6, mixture of diastereomers): δ 177.5, 173.7, 172.0, 171.7, 168.8, 160.5, 156.8, 140.5, 129.7 (2 carbons), 127.3 (2 carbons), 127.0, 124.2, 119.2 (2 carbons), 114.0 (2 carbons), 90.5, 69.2, 60.8, 59.7, 56.5, 41.8, 39.8, 33.6, 29.2, 25.3, 21.9, 15.9, 15.5, 10.4. HRMS (MALDI-TOF, [M + Na^+]): calcd, 639.2543; found, 639.2548.

10m. Crude yield, 125 mg, 91%; crude purity, 95%. HPLC-purified ~4:1 mixture of diastereomers: purity = 99.77%, t_R = 16.79 min; LRMS (ESI, [M + H^+]): 667.15, 669.02. IR (neat): 3413, 3361, 3275, 3256, 2366, 2340, 2284, 1672, 1658, 1605, 1583, 1531, 1490, 1456, 1430, 1412, 1367, 1300, 1237, 1207, 1188 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of diastereomers): δ 10.28 and 10.23 (s, 0.8H and 0.2H), 8.89 (s, 1H), 7.91 (s, 2H), 7.73 (d, 2H, J = 8.4 Hz), 7.63 (d, 2H, J = 8.4 Hz), 7.44 (d, 2H, J = 7.8 Hz), 7.12 (d, 1H, J = 30.4 Hz), 6.92 (d, 2H, J = 8.4 Hz), 4.81 (q, 2H, J = 15.6, 50 Hz), 4.31 (t, 1H, J = 8.8 Hz), ~4.22 to 4.19 (m, 1H), ~4.00 to 3.79 (m, 2H), 3.54 (q, 2H, J = 16 Hz), ~2.44 to 2.01 (m, 6H), ~1.29 to 1.19 (m, 2H), 0.82 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): δ 177.3, 173.4, 171.6, 171.3, 166.8, 157.2, 156.5, 140.4, 131.9 (2 carbons), 127.2 (2 carbons), 124.0, 119.1 (2 carbons), 117.0 (2 carbons), 112.4, 90.5, 66.2, 60.0, 56.3, 55.6, 41.8, 39.8, 33.4, 29.1, 25.2, 15.9, 15.3. HRMS (MALDI-TOF, [M + Na^+]): calcd, 689.1335, 691.1315; found, 689.1337, 691.1318.

10n. Crude yield, 109 mg, 82%; crude purity, 95%. HPLC-purified ~4:1 mixture of diastereomers: purity = 96.95%, t_R = 16.99 min; LRMS (ESI, [M + H^+]): 641.19. IR (neat): 3420, 3376, 3316, 3059, 2362, 2328, 2041, 1919, 1669, 1635, 1605, 1527, 1434, 1415, 1371, 1326, 1255, 1162, 1113, 1069 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of diastereomers): δ 10.29 and 10.23 (s, 0.8H and 0.2H), 8.93 (s, 1H), 7.91 (s, 2H), ~7.74 to 7.61 (m, 4H), 7.48 (d, 2H, J = 8.0 Hz), 7.24 (s, 1H), 7.16 (s, 1H), 4.32 (t, 1H, J = 7.6 Hz), 4.22 (q, 1H, J = 4.8 Hz), 4.01 (d, 1H, J = 11.6 Hz), 3.86 (s, 2H), 3.75 (d, 1H, J = 11.6 Hz), 3.52 (q, 2H, J = 18.6 Hz), ~2.42 to 1.99 (m, 6H), ~1.30 to 1.18 (m, 2H), 0.83 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): δ 177.4, 173.5, 171.7, 171.6, 169.2, 156.5, 140.4 (2 carbons), 139.8, 139.1, 130.5, 129.9 (3 carbons), 127.3, 127.2, 125.6, 125.1, 125.0, 124.0, 119.2, 90.4, 59.9, 56.3, 41.8, 39.8, 33.5, 29.1, 25.2, 16.0, 15.2. HRMS (MALDI-TOF, [M + Na^+]): calcd, 663.2155; found, 663.2150.

10o. Crude yield, 109 mg, 87%; crude purity, 96%. HPLC-purified ~4:1 mixture of diastereomers: purity = 99.37%, t_R = 16.46 min; LRMS (ESI, [M + H^+]): 607.14. IR (neat): 3472, 3420, 3271, 3066, 2366, 2332, 2198, 2183, 2161, 2030, 2015, 1986, 1680, 1669, 1635, 1609, 1523, 1494, 1438, 1415, 1371, 1307, 1255, 1199, 1181, 1158, 1091 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of diastereomers): δ 10.29 and 10.23 (s, 0.8H and 0.2H), 8.92 (s, 1H), 7.91 (s, 2H), 7.73 (d, 2H, J = 8.4 Hz), 7.61 (d, 2H, J = 8.0 Hz), 7.37 (d, 2H, J = 7.2 Hz), 7.27 (d, 2H, J = 7.6 Hz), 7.16 (s, 1H), 4.30 (t, 1H, J = 8.4 Hz), 4.21 (q, 1H, J = 4.4 Hz), 3.97 (d, 2H, J = 11.6 Hz), 3.73 (s, 2H), 3.50 (q, 2H, J = 18.4 Hz), ~2.41 to 2.01 (m, 6H), ~1.30 to 1.19 (m, 2H), 0.82 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): δ 177.4, 173.5, 171.8, 171.5, 169.5, 156.5, 140.4, 139.1, 133.8, 131.4, 131.1, 130.9 (2 carbons), 128.2 (2 carbons), 127.9, 127.2, 124.0, 119.2, 90.4, 59.9, 57.1, 56.3, 41.8, 39.8, 33.4, 29.1, 25.2, 16.0, 15.2. HRMS (MALDI-TOF, [M + Na^+]): calcd, 629.1891; found, 629.1889.

10p. Crude yield, 114 mg, 86%; crude purity, 98%. HPLC-purified ~4:1 mixture of diastereomers: purity = 97.10%, t_R = 19.36 min; LRMS (ESI, [M + H^+]): 642.25. IR (neat): 3465, 3352, 3304, 3095, 2359, 2321, 1666, 1614, 1581, 1543, 1495, 1429, 1348, 1315 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of diastereomers): δ 11.02 and 10.98 (s, 0.2H and 0.8H), 9.19 (s, 2H), 9.03 (s, 2H), 8.11 (s, 1H), 7.94 (s 2H), ~8.14 to 7.12 (m, 8H), ~4.57 to 4.53 (m, 1H), ~4.09 to 4.06 (m, 1H), 3.97 (d, 2H, J = 12.0 Hz), 3.57 (q, 2H, J = 17.6 Hz), 2.91 (s, 1H), 2.75 (s, 1H), ~1.33 to 1.25 (m, 2H), 0.89 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): δ 178.9, 173.5, 171.7, 168.9, 161.4, 157.0, 148.0 (2 carbons), 138.6, 137.1, 135.1, 130.5, 129.6, 129.3, 128.3, 128.0 (3 carbons), 127.3, 122.8, 122.2, 121.2, 118.1, 90.7, 65.8, 60.4, 41.8, 39.8, 33.5, 15.8, 15.3. HRMS (MALDI-TOF, [M + Na^+]): calcd, 664.1768; found, 664.1766.

10q. Crude yield, 129 mg, 89%; crude purity, 97%. HPLC-purified ~4:1 mixture of diastereomers: purity = 98.12%, t_R = 20.62 min; LRMS (ESI, [M + H^+]): 700.34. IR (neat): 3463, 3312, 3260, 3212, 3104, 2973, 2932, 2880, 2362, 2340, 2276, 1672, 1605, 1542, 1486, 1430, 1412, 1345, 1311 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of diastereomers): δ 10.98 (s, 1H), 9.20 (s, 2H), 9.02 (s, 1H), 8.11 (s, 1H), 7.94 (s, 2H), ~7.66 to 7.01 (m, 8H), ~4.54 to 4.50 (m, 0.5H), ~4.14 to 4.11 (m, 0.5H), 3.99 (s, 2H), 3.76 (s, 1H), 3.57 (q, 1H, J = 17.6 Hz), 2.91 (s, 1H), 2.75 (s, 1H), 2.31 (s, 1H), ~1.78 to 1.72 (m, 1H), 1.32 (m, 2H), 1.24 (m, 2H), 0.99 (t, 3H, J = 7.2 Hz), 0.89 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): δ 173.5, 171.8, 168.6, 161.3, 160.3, 157.0, 148.0 (2 carbons), 138.6, 137.0, 129.7, 129.6 (2 carbons), 129.3, 127.9 (2 carbons), 126.8, 122.8, 122.2, 121.2, 118.1, 113.9 (2 carbons), 90.8, 69.0, 60.6, 59.4, 41.8, 39.8, 33.5, 21.8, 15.8, 15.3, 10.2. HRMS (MALDI-TOF, [M + Na^+]): calcd, 722.2187; found, 722.2183.

10r. Crude yield, 133 mg, 86%; crude purity, 98%. HPLC-purified ~4:1 mixture of diastereomers: purity = 96.03%, t_R = 20.58 min; LRMS (ESI, [M + H^+]): 750.18, 752.29. IR (neat): 3424, 3301, 3100, 3059, 2958, 2928, 2880, 2362, 2340, 2325, 1669, 1609, 1542, 1486, 1434, 1412, 1345, 1307 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of diastereomers): δ 11.02 (s, 1H), 9.21 (s, 2H), 9.03 (s, 1H), 8.19 (s, 2H), 7.96 (s, 2H), ~7.57 to 7.44 (m, 3H), 7.18 (s, 1H), 7.11 (s, 1H), ~7.01 to 6.90 (m, 2H), ~4.94 to 4.74 (m, 2H), ~4.38 to 4.34 (m, 1H), ~3.93 to 3.87 (m, 1H), 3.61 (q, 1H, J = 17.8 Hz), 2.91 (s, 1H), 2.75 (s, 1H), ~2.23 to 2.18 (m, 2H), ~1.29 to 1.24 (m, 2H), 0.85 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): δ 173.4, 171.3, 166.8, 161.4, 161.4, 157.2, 156.9, 148.0 (2 carbons), 138.7, 137.0, 131.9 (2 carbons), 129.6, 129.3, 128.0 (2 carbons), 122.3, 121.2, 118.1, 117.0 (2 carbons), 112.4, 90.8, 66.3, 60.0, 55.6, 41.8, 39.8, 33.5, 15.9, 15.3. HRMS (MALDI-TOF, [M + Na^+]): calcd, 772.0979, 774.0958; found, 772.0974, 774.0973.

10s. Crude yield, 122 mg, 82%; crude purity, 93%. HPLC-purified ~4:1 mixture of diastereomers: purity = 96.71%, t_R = 20.74 min; LRMS (ESI, [M + H^+]): 724.30. IR (neat): 3461, 3301, 3100, 3059, 2958, 2928, 2880, 2362, 2340, 2325, 1665, 1613, 1542, 1497, 1434, 1415, 1345, 1326 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, mixture of diastereomers): δ 11.00 (s, 1H), 9.20 (s, 2H), 9.02 (s, 1H), 8.16 (s, 2H), 7.95 (d, 2H, J = 6.8 Hz), 7.69 (d, 2H, J = 8.0 Hz), ~7.55 to 7.41 (m, 3H), 7.23 (s, 1H), 7.16 (s, 1H), 4.33 (t, 1H, J = 8.8 Hz), ~4.05 to 3.78 (m, 1H), 3.87 (s, 2H), 3.57 (q, 1H, J = 17.6 Hz), 2.89 (s, 1H), 2.73 (s, 1H), ~2.46 to 2.40 (m, 1H), ~2.21 to 2.12 (m, 1H), ~1.30 to 1.18 (m, 2H), 0.83 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): δ 172.7, 169.7, 168.2, 160.8, 156.3, 147.3 (2 carbons), 138.4, 136.9, 135.5, 130.0, 129.5, 128.8 (3 carbons), 128.5, 125.9 (2 carbons), 124.0, 123.9, 122.1, 120.6, 119.1, 117.7, 117.6, 90.8, 59.5, 56.6, 41.8, 39.8, 32.7, 16.4, 14.9. HRMS (MALDI-TOF, [M + Na^+]): calcd, 746.1798; found, 746.1797.

10t. Crude yield, 120 mg, 84%; crude purity, 96%. HPLC-purified ~4:1 mixture of diastereomers: purity = 97.22%, t_R = 20.30 min; LRMS (ESI, [M + H^+]): 690.24. IR (neat): 3480, 3301, 3096, 2940, 2321, 2265, 1665, 1623, 1613, 1542, 1494, 1434, 1408, 1345 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, mixture of diastereomers): δ 11.04 and 11.00 (s, 0.2H and 0.8H), 9.19 (s, 2H), 9.02 (s, 1H), 8.92 (s, 1H), 8.16 (s, 2H), 7.95 (d, 2H, J = 6.8 Hz), ~7.55 to 7.35 (m, 3H), ~7.28 to 7.22 (m, 2H), 7.15 (s, 1H), 4.31 (t, 1H, J = 8.0 Hz), ~4.01 to 3.71 (m, 1H), 3.74 (s, 2H), 3.55 (q, 1H, J = 18.0 Hz), 2.89 (s, 1H), 2.73 (s, 1H), ~2.44 to 2.39 (m, 1H), ~2.20 to 2.14 (m, 1H), ~1.30 to 1.18 (m, 2H), 0.83 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of diastereomers): δ 173.5, 171.7, 169.5, 161.4, 156.9, 148.1 (2 carbons), 138.6, 137.1, 133.8, 131.4, 131.1, 130.9 (2 carbons), 129.6, 129.3, 128.1 (2 carbons), 128.0 (2 carbons), 122.8, 122.2, 121.2, 118.1, 90.8, 59.8, 57.0, 41.8, 39.8, 33.4, 16.0, 15.2. HRMS (MALDI-TOF, [M + Na^+]): calcd, 712.1535; found, 712.1536.

Synthesis of Encoded Small Molecule Library. Library synthesis was initiated by swelling TentaGel S NH_2 resin (5.0 g, 0.26 mmol/g loading capacity) in water with shaking for 48 h. Fmoc-OSu (0.1 equiv), dissolved in DCM/Et_2O (55:45, v/v) was added to a sealable vessel containing the resin, followed by the addition of DIEA (2.0 equiv). This vessel was vigorously shaken for 30 min, after which the solution was drained, and the resin was transferred to a disposable plastic column. The resin was washed with the following standard washing procedure: DMF (3 times), water (3 times), MeOH (3 times), DCM (5 times), and DMF (2 times). The resin was then treated with di-*tert*-butyl dicarbonate (1.1 equiv) dissolved in DMF containing DIEA (2 equiv). The Fmoc group found on the surface of the resin was removed by treatment with 20% piperidine in DMF two times for 10 min. 2-Bromoacetic acid (10 equiv) was then dissolved in DMF containing HOBt (15 equiv), and DIC (15 equiv) was added to this mixture to preactivate the carboxylic acid. After the reaction solution had mixed for 30 min, the solution was added to the resin, and the reaction was allowed to proceed for 30 min, at which time the Kaiser test indicated the disappearance of the primary amine. The solutions were drained, the resin was washed, and a solution of piperazine (10 equiv) in DMF containing DIEA (15 equiv) was added. The displacement reaction was allowed to proceed for 16 h. A solution of Fmoc-OSu (0.25 equiv) in DMF containing DIEA (0.5 equiv) was then added to the resin to protect the secondary amine. Boc deprotection was then undertaken using a solution of TFA/water/TIS (95:2.5:2.5, v/v/v) for 30 min, after which the resin was washed, and Boc-Lys(Dde)−OH (3 equiv) and HOBt (3.5 equiv) dissolved in DMF was added to the resin, followed by DIC (3.5 equiv). The mixture was allowed to react until the Kaiser test indicated completion, at which time the resin was drained and washed, and the Boc group was removed with the cleavage solution described above. The process was repeated with Boc-Phe-(4-NO_2)−OH, HOBt, and DIC until the Kaiser test indicated reaction completion and another Boc deprotection was performed. The resin was then distributed into 96 columns, and a solution of two Boc protected amino acid coding blocks were coupled using the methods described above drawing from a standard solution of 0.4 M Boc-AA(P)−OH in DMF according to the ratios of relative reactivity, which can be found in the Supporting Information.

When all Kaiser tests were negative, the resin remained distributed, and an Fmoc deprotection was performed as described above. Once complete, the testing amino acids, Fmoc-X−OH (3 equiv), were coupled to the growing target molecule using HOBt and DIC (3.5 equiv each). Once this coupling was complete, the resin was mixed and washed, and compounds **7a** and **b** (4:1, 0.25 equiv) were coupled to the surface molecule using HOBt and DIC (0.5 equiv each). The arylnitro group was reduced with $SnCl_2 \cdot 2H_2O$ (30 equiv) in DMF, which was added to the resin, and the reduction was allowed to proceed for 2 h, after which the resin was drained, washed, and distributed to 30 different plastic columns in which the coupling of the first carboxylic acid diversity element was undertaken under the following conditions: R_1-CO_2H (10.0 equiv), HOBt (13.0 equiv), and DIC (13.0 equiv) in DMF. This acylation was allowed to proceed until the modified chloranil test[35] showed the reaction to be complete. An Fmoc and Dde deprotection was performed with 2% hydrazine in DMF (2 times, 10 min each) that delivered the free amines that were acylated with the second carboxylic acid diversity element according to the following procedure: R_2-CO_2H (10.0 equiv), HOBt (13.0 equiv), DIC (13.0 equiv) in DMF. This acylation was allowed to proceed until a standard chloranil test showed the reaction to be complete.

The final deprotection of all acid-sensitive protecting groups was performed with TFA/phenol/TIS/water/EDT (90:5:2:2:1, v/w/v/v/v), which was incubated with the resin for 2 h. After the cleavage was complete, the TFA mixture was drained, and the resin was washed thoroughly with water (5 times), MeOH (7 times), DCM (10 times), MeOH (10 times), and water (10 times). Upon the final wash, the resin was placed in a PBS buffer (1×) with 0.1% NaN_3 and stored under refrigeration until needed.

Edman Degradation Sequencing. The sequencing of the encoding peptide tags was performed on an ABI 494 Protein

Sequencer using a modified program and gradients described in the literature.[36]

Abbreviations

EtOAc, ethyl acetate; MeOH, methanol; DCM, dichloromethane; THF, tetrahydrofuran; NaOAc, sodium acetate; Fmoc-OSu, *N*-(9-fluorenylmethoxycarbonyloxy) succinimide; DMF, *N*,*N*-dimethylformamide; HOBt, *N*-hydroxybenzotriazole; DIC, diisopropylcarbodiimide; DMSO, dimethylsulfoxide; TIS, triisopropylsilane; TFA, trifluoroacetic acid; TEA, triethylamine; LC/MS, liquid chromatography/mass spectrometry; EDT, ethanedithiol; Et_2O, diethyl ether; DIEA, diisopropylethylamine; PBS, phosphate-buffered saline; Dde, 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl.

Acknowledgment. The authors thank the National Science Foundation (CHE-0614756) and the National Institutes of Health (GM076151). The authors also thank Dr. Alan Lehman for editorial assistance and Dr. Amanda Enstrom for assistance with MALDI-TOF analyses.

Supporting Information Available. ^{1}H NMR for compounds **1**−**6**, **7a**, **7b**, **8**−**9**, and **10a**−**10t**. ^{13}C NMR spectra for compounds **1**−**6**, **7a**, **7b**, **8**−**9**, **10a**−**10g**, and **10i**−**10t**. Diversity elements and other important information used in library synthesis. A sample Edman degradation with interpretation and target molecule identified. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC060090P