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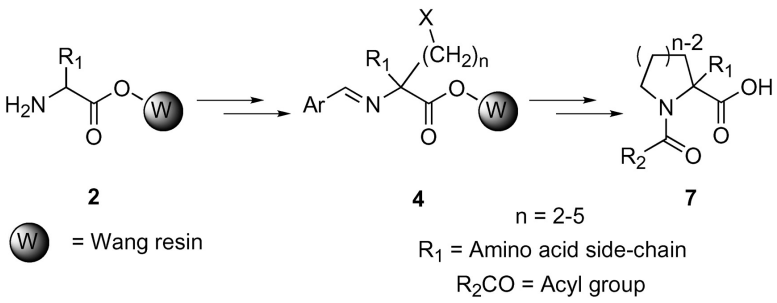

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The Manual and Automated Solid-Phase Synthesis of α-Substituted Prolines and Homologues

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Activation of N-terminal resin-bound amino acids as aldimines, followed by alkylation with α,ω-dihaloalkanes, provides key intermediates for the solid-phase preparation of racemic α-substituted proline ring homologues bearing amino acid side chains. Two intramolecular displacement strategies, one involving an amine nucleophile, the other an amide nucleophile, were used to convert the intermediate ω-chloro or ω-bromo derivatives to the desired cyclic products. Using one of these routes and a fully automated synthesizer, a 48-membered library of α-substituted prolines was prepared in a combinatorial fashion.

Introduction

Proline is special among the 20 naturally occurring amino acids. Its cyclic, secondary amine structure has two unique consequences on proline-containing peptides, proteins, and drugs. First, there can be present, at equilibrium, major amounts of the usually minor cis (ω) amide rotamer.[1] Second, its cyclic nature imposes a fixed orientation on the normally freely rotatable N−Cα ("φ") bond. Both of these features play an important role in determining the local and global three-dimensional shape of molecules containing proline (see Figure 1).

Conformationally constrained analogues of peptides containing proline have been prepared primarily to restrict these backbone conformations.[2] By preparing analogues and homologues of proline in which the α-carbon now bears other amino acid side chains, we could restrict not only backbone conformations but also, at its source, one of the key torsional bonds responsible for multiple amino acid side-chain orientations.[3] Therefore, we sought to develop a general solid-phase route to hybrid molecules of structure **1** (see Figure 2),[4] in which R_1 could be many of the naturally occurring side chains and the N−Cα (φ) bond torsional angle could be finely tuned by varying the ring size from 4 to 7.[5,6] These conformationally restricted amino acid analogues could then be used in both mechanistic and drug discovery programs. In this work, we describe the manual synthesis of resin-bound derivatives of four- to seven-membered α-substituted proline ring homologues **1** ($n = 2-5$, $R_1 = CH_3$) and an automated solid-phase synthesis of α-substituted prolines incorporating eight different amino acid side chains R_1.

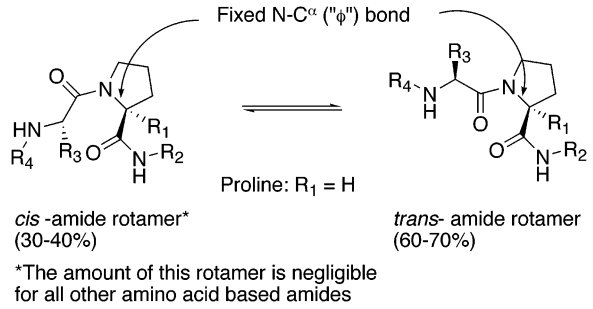

Figure 1. Unique conformational aspects of proline-containing dipeptides.

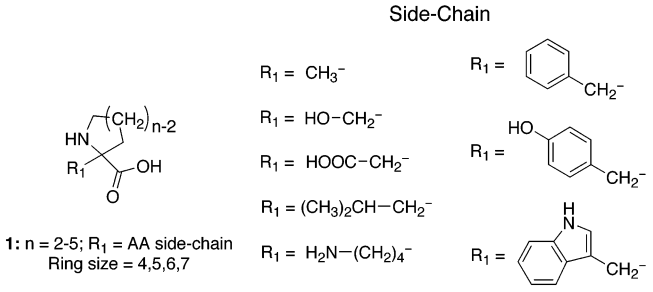

Figure 2. Generic structure for potential α-substituted proline ring homologues incorporating various amino acid side chains.

Results and Discussion

We recently published solid-phase methodology to unnatural amino acids with diverse side-chain substitutions.[7] In the course of that work, we prepared the intermediate **5** (R_1 = methyl, $n = 3$, X = Cl), which, upon neutralization, rapidly cyclized to the five-membered proline derivative **6** (R_1 = methyl, $n = 3$, see Scheme 1). We recognized that with the appropriate ω-activated precursor, it should be possible to generalize this facile cyclization to the four-, six-, and seven-membered rings. On the basis of our successful di-UPS (disubstituted *u*nnatural *p*eptide *s*ynthesis) chemistry,[8]

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Scheme 1. Synthesis of Resin-Bound α-Substituted Proline Homologues by Strategy 1

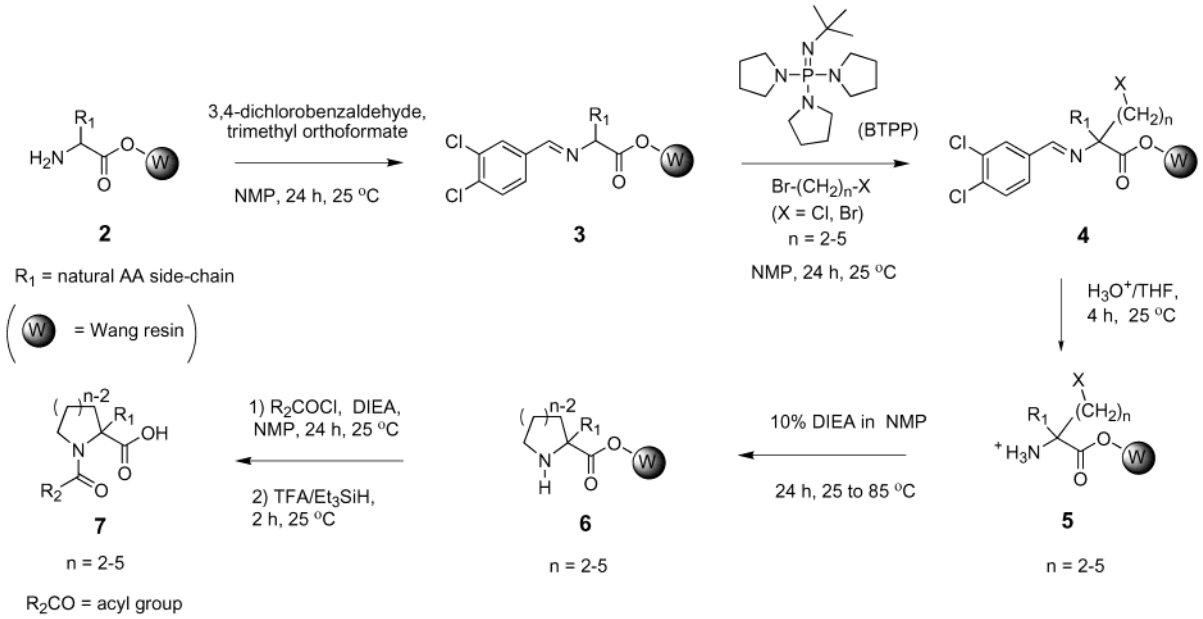
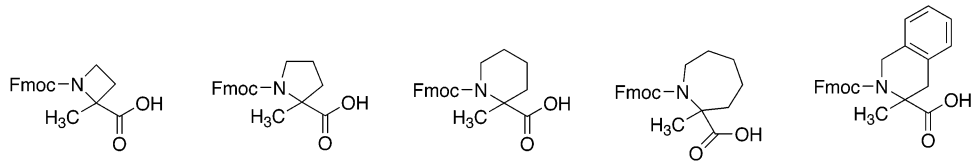


Table 1. Preparation of N^{α}-Fmoc α-Substituted Proline Homologues via Strategy 1



	7a	7b	7c	7d	7e
Crude HPLC Purity	66%	92%	91%	89%	94%
Purified Yield	26%	68%	69%	73%	65%
Halide precursor	Cl	Cl	Cl	Br	Cl

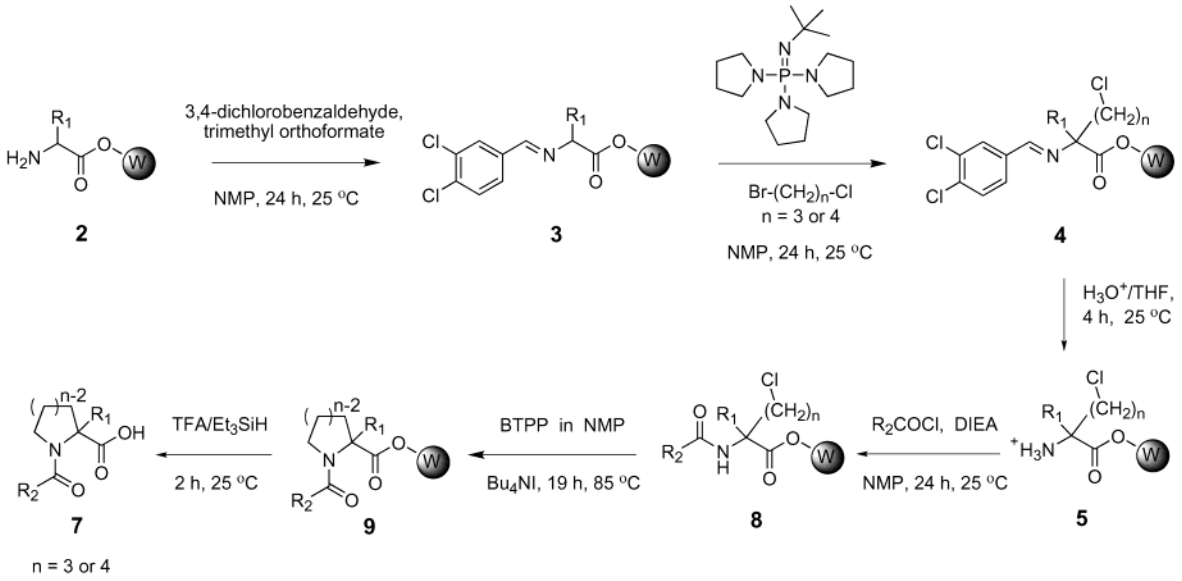
it would also be possible to obtain varied α-R_1 groups with both unnatural and natural amino acid side chains. The general route to these molecules using the first of our synthetic strategies is shown in Scheme 1.

Strategy 1: Intramolecular Displacement of the ω-Halide by the α-Amino Group (Scheme 1). As a representative example, commercially available Fmoc-Ala−Wang resin (R_1 = CH_3) was deprotected using standard procedures (20% piperidine in DMF) to generate the resin-bound free α-amine **2**, which was converted to the aldimine **3** by condensation with 3,4-dichlorobenzaldehyde in the presence of trimethyl orthoformate. Alkylation of the activated intermediate **3** with α,ω-dihaloalkanes of different chain lengths ($n = 2-5$) led to the formation of key resin-bound racemic intermediates **4**. This alkylation was carried out in NMP using the strong nonionic Schwesinger base BTPP[9,10] for proton abstraction from the α-carbon. In most cases, α-bromo-ω-chloro electrophiles were used instead of α,ω-dibromo electrophiles in order to reduce side reactions during alkylation and subsequent transformations.[11] Imine intermediates **4** were then hydrolyzed to the resin-bound amine salts **5**. Formation of α-substituted proline ring homologues **6** was carried out by neutralization and intramolecular displacement of the halide by the α-amino group. Cyclizations were carried out in a 10% solution of *N*,*N*-diisopropylethylamine (DIEA) in NMP for 24 h. The temperature used depended on the ring size. Cyclization was complete at room temperature for $n = 3$ (five-membered ring) and $n = 4$ (six-membered ring) using ω-chloro intermediates. For $n = 5$ (seven-membered ring) cyclization required higher temperatures: either 85 °C using ω-bromo or 120 °C using ω-chloro intermediates. For $n = 2$, four-membered ring formation using the ω-chloro derivative also required higher temperature (85 °C) and the presence of 10 equiv of tetrabutylammonium iodide.[12] The cyclic secondary amine products **6** were then converted to the resin-bound Fmoc amino acid derivatives using a 10-fold excess of 9-fluorenylmethyl chloroformate (Fmoc-Cl) in the presence of DIEA. Final cleavage from the resin with TFA/triethylsilane (TES)[13] gave the desired N-protected products **7** (Scheme 1 and Table 1). Initial HPLC purities (UV detection at 220 nm) of the crude products **7a**−**d** were from 66 to 92%, with purified, isolated yields from 26 to 73% (purification by silica gel chromatography).

It is worth noting that α-substituted tetrahydroisoquinoline carboxylic acids[14] can also be prepared by this procedure. For example, the alanine-derived N^{α}-Fmoc 3-methyl-1,2,3,4-tetrahydroisoquinolino 3-carboxylic acid (Table 1, **7e**) was prepared following the same protocols previously described by using α,α′-dichloro-*o*-xylene as the alkylating agent[15] and 10% DIEA in NMP for 24 h at room temperature for the intramolecular cyclization. HPLC purity of the crude product was 94%, with a purified yield of 65%.

Strategy 2: Intramolecular Displacement of the Halide by an Amide Nitrogen (Scheme 2). This route, which was

Scheme 2. Synthesis of N-Acylated α-Substituted Proline Homologues by Strategy 2.



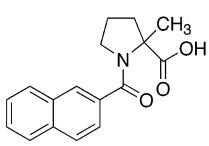
studied for cases $n = 3$ or 4, provides an alternative synthesis of α-substituted proline homologues **9**. The N-acylated chloro-substituted amino acid derivatives **8** were prepared and then cyclized to the α-substituted proline ring homologues **9** by displacement of the halide by the nitrogen of the amide. In this case, resin-bound amine salt **5** was first converted to the resin-bound N-acylated chloro-substituted derivative **8**. This was accomplished with a 10-fold excess of 2-naphthoyl chloride with an in situ neutralization protocol to minimize the competing intramolecular cyclization reaction. At this stage, a small aliquot of resin was cleaved using TFA/TES in order to determine the amount of premature cyclization. This was assessed by determining the ratio of acyclic naphthoyl chloro product from cleaved **8** to the cyclic naphthoyl derivative from cleaved **9**. Not surprisingly, when $n = 3$, substantial premature cyclization occurred to the favored five-membered ring. This was indicated by a ratio of 48:52 cleaved **8** to cleaved **9**. However, for $n = 4$, only a small amount (4% cleaved **9**) of premature cyclization occurred to the six-membered ring.

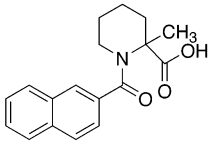
The intended intramolecular cyclization of **8** to form **9** was accomplished using 10 equiv each of BTPP and tetrabutylammonium iodide in NMP for 19 h at elevated temperature (85° C).[16] After final TFA cleavage from the resin,[17] HPLC purity of the crude products **7f** and **7g** were 92 and 93%, with purified, isolated yields of 77 and 49%, respectively. See Table 2 for comparative results between the two strategies.

Library Synthesis. A seven step fully automated synthesis of a 48-member combinatorial library (50-μmol scale) of α-substituted prolines was carried out by strategy 1 using an Argonaut Technologies Trident Library Synthesizer. Automated procedures were based on the manually optimized methods described previously. Eight different commercially available Wang polystyrene resins preloaded with N^{α}-Fmoc-protected amino acids and six different acyl chlorides were chosen as diversity reagents.

After TFA-mediated cleavage from the resins, aliquots of each sample of the library were analyzed by reversed-phase HPLC and electrospray MS. Purification of the crude samples was carried out using automated reversed-phase chromatography. Table 3 shows structures, HPLC purities, and purified yields of products corresponding to two of the six acylation rows of the 8 × 6 run.

Table 2. Structures, Purities, and Yields of **7f** and **7g** by Strategies 1 and 2





	7f		**7g**	
	Strategy 1	Strategy 2	Strategy 1	Strategy 2
Crude HPLC Purity	89%	92%	92%	93%
Purified Yield	71%	77%	69%	49%

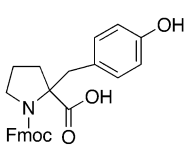
Excluding the tryptophan series, all of the crude products had an initial HPLC purity of >80% and were isolated with an overall average purified yield of 40%. In all cases, there was no evidence of unreacted starting amino acid. The side-chain protecting groups Asp(O^tBu), Lys(Boc), Ser(^{t}Bu), Trp(Boc), and Tyr(^{t}Bu) were compatible with the alkylation, hydrolysis, cyclization, and acylation conditions as previously observed in our di-UPS work.[8b] As expected, for tryptophan and serine, problems arose in the cleavage step: (1) in the case of tryptophan, very low HPLC purities and purified yields were obtained for all derivatives (e.g., **10b** and **10j**) because of partial reduction of the indole ring to an indoline by the Et_3SiH in the cleavage mixture; (2) for serine, the purified yield of derivative **10k** was somewhat lower because of partial *N*- to *O*-acyl migration under acidic conditions.[18]

Conclusions

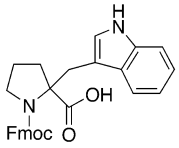
In summary, the alkylation of aldimine derivatives of resin-bound amino acids with α,ω-dihaloalkanes provides access to key intermediates for the solid-phase synthesis of racemic α-substituted proline homologues (ring size 4−7) bearing amino acid side chains. Two strategies were developed to

Table 3. Structures, Purities, and Yields of Representative Examples of a 48-Compound Library of α-Substituted Prolines Prepared by Strategy 1 Using Automated Procedures[a]

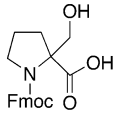
Fmoc Row



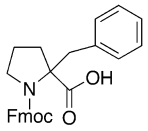
10a (>90%, 52%)



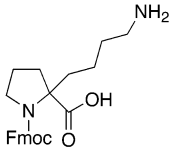
10b (>50%, -)



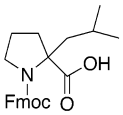
10c (>80%, 34%)



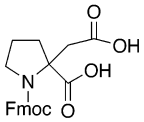
10d (>95%, 35%)



10e (>95%, 48%)



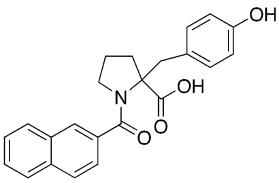
10f (>90%, 44%)



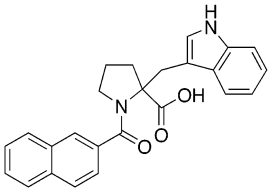
10g (>90%, 42%)

10h (>85%, 41%)

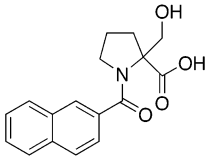
Naphthoyl Row



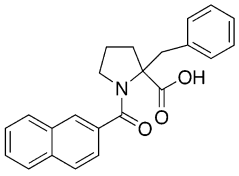
10i (>85%, 44%)



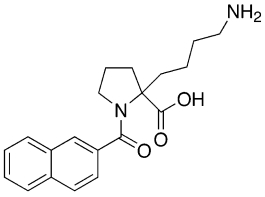
10j (>30%, 7%)



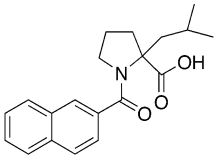
10k (>85%, 28%)



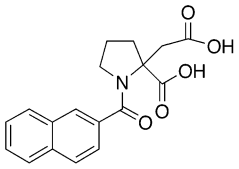
10l (>90%, 28%)



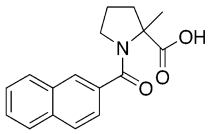
10m (>90%, 48%)



10n (>95%, 39%)



10o (>90%, 39%)



10p (>90%, 45%)

[a]Compound Number (Crude HPLC purity, Purified Yield). See text for discussion

transform the ω-chloro or ω-bromo derivatives to the desired products. A manually optimized method was then employed in a fully automated synthesis of a 48-member library of α-substituted prolines. Optimized conditions for strategy 2 (displacement of the ω-halide by the nitrogen of an amide) are currently being used in our laboratory for the solid-phase preparation of lactam-based peptidomimetics.

Experimental Section

General Methods. All reactions and washes were conducted at ambient temperature unless indicated otherwise. Fmoc-AA−Wang resins and 9-fluorenylmethyl chloroformate were obtained from NovaBiochem. Anhydrous NMP and DMF, piperidine, trimethyl orthoformate, 3,4-dichlorobenzaldehyde, 1-bromo-2-chloroethane, 1-bromo-3-chloropropane, 1-bromo-4-chlorobutane, 1,5-dibromopentane, α,α′-dichloro-*o*-xylene, *N*,*N*-diisopropylethylamine, 2-naphthoyl chloride, trifluoroacetic acid, and triethylsilane were purchased from Aldrich Chemical Co. BTPP (*tert*-butylimino-tri(pyrrolidino)phosphorane) and tetrabutylammonium iodide were purchased from Fluka. Manual solid-phase organic syntheses were carried out at 25 °C in polypropylene syringes equipped with a porous polypropylene disk at the bottom (purchased from Torviq, Catalog no. SF-0500). Solid-phase reactions at higher temperatures were carried out in Pyrex brand tubes with Teflon fluorocarbon resin-faced rubber-lined caps (purchased from Fisher Scientific, Catalog no. 14-933C). Silica gel flash chromatography was performed with silica gel 60 (230−400 mesh) from Silicycle. Analytical HPLC was performed using a Waters C_{18} reversed-phase column (3.9 × 150 mm) on a Varian 9010 instrument, and linear gradients of 0.1% TFA in CH_3CN and 0.1% aqueous TFA were run at 1.0 mL/min flow rate from 0:1 to 1:0 over 25 min. UV detection was at 220 nm. NMR analyses were performed using a GE QE 300-MHz NMR. Chemical shifts (δ) are in ppm. Electrospray ionization mass spectrometry was conducted using a PESciex API III triple stage quadrupole mass spectrometer operated in the positive ion detection mode. High-resolution mass spectrometry was run in the FAB mode. The yields of final compounds, after chromatographic purification, are calculated on the basis of the initial loading of the starting Wang resins and are the overall yields of all reaction steps starting from these resins.

Comment on the Compiled Spectral Data. For several compounds, there were a different number of ^{13}C resonances from that predicted by simple models. These examples can be classified in three categories: (a) For compound **7a**, one of the quaternary carbons of the Fmoc system gave separate

signals (δ 143.3 and 143.4) because of nonequivalency. For compound **7c**, the two quaternary carbons (δ 142.6, 142.7, 145.2, and 145.4) and one of the CH aromatic carbons (δ 126.0 and 126.1) of the Fmoc system gave separate signals because of nonequivalency. Similarly results were observed for compounds **7d** and **7e**. (b) For compound **7b**, some of the carbons gave doubled signals because of the presence of two nitrogen rotamers. (c) For compound **7g**, too few ^{13}C resonances were observed because of overlap of one of the CH aromatic signals.

Manual Procedures

General Procedures for Parallel Solid-Phase Reactions. Manual solid-phase organic syntheses were carried out at 25 °C in polypropylene syringes (disposable reaction vessels) equipped with porous polypropylene disks at the bottom. Syringes of 5-mL volume were used on the basis of the quantity of initial dried resin (200 mg). Typically, the syringe was charged with resin, and then the solvent used in the following reaction was added to create a slurry. The resin beads were washed with this solvent (3 mL of solvent per 1 mL of swollen resin). The mixture was stirred using a capillary tube for a given time, and after finishing the treatment, the solvent was removed by filtration using a vacuum system.

Introduction of Reagents. Prior to the addition of reagents, the bottom part of the syringe was capped using a septum, then solvents and reagents were added. After manual stirring with a capillary tube for 2 min, the plunger was placed at the top of the syringe. Removal of the septum allowed for modification of the volume of the reaction vessel by moving the plunger to the desired position. After replacing the septum, the reaction vessel was mixed by gentle rotation using a rotary evaporator or mechanical stirrer.

Higher Temperature Reactions. Solid-phase reactions at higher temperatures (85 °C) were carried out in Pyrex brand tubes with Teflon fluorocarbon resin-faced rubber-lined caps. In these experiments, after washing the resin using the syringe system as above, the resin was transferred to the glass tube using the total amount of solvent needed for the reaction. Reagents were added, and after the cap was replaced, the reaction vessel was placed in a sand bath for the given time with occasional manual agitation. After the reaction was completed, the reaction mixture was transferred to a syringe and treated as above.

Automated Procedures

Fully automated parallel library synthesis was carried out with an Argonaut Technologies Trident Library Synthesizer. This machine is capable of running up to 192 reactions in parallel. The main part of the system is the Trident Reaction Cassette that holds 48 5-mL glass vessels. These reaction vessels have a Teflon cap that rotates to open and close a delivery port and a vent port. Trident software allows control of the temperature, agitation, reagent/solvent deliveries, and product collection.

Manual Synthesis: Strategy 1

Preparation of the 3,4-Dichlorobenzaldehyde Imine of Ala−Wang Resin. In a 5-mL syringe, Fmoc-Ala−Wang resin (0.200 g, 0.84 mmol/g) was washed with CH_2Cl_2 (2 × 4 mL, 1 min each) and DMF (2 × 4 mL, 1 min each) and then treated with piperidine−DMF (1:4, 3 × 4 mL, 5 min each), followed by washings with DMF (6 × 4 mL, 0.5 min each). 3,4-Dichlorobenzaldehyde (441 mg, 15 equiv) was dissolved in NMP−TMOF (1:2, 3 mL total) and added to the resin, and the reaction was allowed to proceed for 24 h with rotation. The resultant resin-bound Schiff base product was washed with NMP (6 × 4 mL, 0.5 min each) and THF (6 × 4 mL, 0.5 min each).

Alkylation of the Benzaldehyde Imine of Ala−Wang Resin with an α,ω-Dihaloalkane. Resin-bound Schiff base (168 μmol) was washed with CH_2Cl_2 (4 × 4 mL, 0.5 min each) and NMP (4 × 4 mL, 0.5 min each). The α,ω-dihaloalkane (10 equiv) in NMP (2.0 mL) and BTPP (515 μL, 10 equiv) were added, and the reaction mixture was rotated for 24 h. The resin was filtered and washed with NMP (6 × 4 mL, 0.5 min each) and CH_2Cl_2 (4 × 4 mL, 0.5 min each).

Hydrolysis of the Imine in the Resin-Bound Alkylated Products. The resin-bound imine (168 μmol) was washed with THF (6 × 4 mL, 0.5 min each). THF/1 N aqueous HCl (2:1, 4 mL) was added, and the reaction mixture was rotated for 4 h. The resin was filtered and washed with THF (6 × 4 mL, 0.5 min each) and CH_2Cl_2 (6 × 4 mL, 0.5 min each).

Intramolecular Cyclization of the Resin-Bound Alkylated Products. The resin-bound amine (168 μmol) was washed with NMP (6 × 4 mL, 0.5 min each) and 10% DIEA in NMP (1 × 4 mL, 1 min). Then, 10% DIEA in NMP (4 mL) was added to the resin, and the reaction mixture was rotated for 24 h. The resin was filtered and washed with NMP (4 × 4 mL, 0.5 min each) and CH_2Cl_2 (4 × 4 mL, 0.5 min each).

Acylation of Resin-Bound Product with Fmoc-Cl. The resin-bound cyclic amine (168 μmol) was washed with NMP (4 × 4 mL, 0.5 min each). Fmoc-Cl (435 mg, 10 equiv) was dissolved in NMP (1.8 mL) and added to the resin, and the acylation was started by addition of DIEA (570 μL, 20 equiv). The reaction mixture was rotated for 24 h. The resin was filtered and washed with NMP (6 × 4 mL, 0.5 min each), DMF (6 × 4 mL, 0.5 min each), THF (6 × 4 mL, 0.5 min each), and CH_2Cl_2 (6 × 4 mL, 0.5 min each).

Cleavage of the Product from the Resin and Final Purification. The resin was cleaved with TFA−triethylsilane (TES) (95:5, 2 × 5 mL, 1 × 2 h, 1 × 30 min). The filtrates from the cleavage reaction were collected, combined with the TFA−CH_2Cl_2 washes (1:3, 2 × 5 mL, 2 min each) of the resin, and evaporated under a stream of argon. The crude residues were redissolved in $CHCl_3$ (1.5 mL) and purified over silica gel with $CHCl_3$−THF−HOAc (92:8:1) to elute the final compounds. After removal of the solvent from the desired fractions, in most cases, the purified products were redissolved in the minimum amount of benzene and precipitated by addition of cold pentane to obtain, after centrifugation/decantation, solid material.

The ^1H NMR spectra of compounds **7a**, **7b**, and **7d** include protons that show fractional integrations. These phenomena reflect slow interconversion of the cis−trans rotational isomers of the urethane C−N bond.

1-(9*H*-Fluoren-9-ylmethyl) Hydrogen 2-Methyl-1,2-azetidine Dicarboxylate (7a). Prepared as described above, using 1-bromo-2-chloroethane (140 μL, 10 equiv) in the alkylation step and tetrabutylammonium iodide (620 mg, 10 equiv) and 10% DIEA in NMP (3 mL) in the intramolecular cyclization (using a glass vessel and heating at 85 °C for 24 h with occasional agitation), to provide an amorphous white solid (14.7 mg, 26% isolated yield) following purification: initial HPLC purity 66%, t_R = 10.8 min. ^{1}H NMR (CD_3OD) [mixture of two nitrogen rotamers, ratio 1.5:1] δ 1.50 (s, 1.8H), 1.68 (s, 1.2H), 2.17−2.50 (m, 2H), 3.75−4.16 (m, 2H), 4.16−4.56 (m, 3H), 7.30−7.50 (m, 4H), 7.62−7.74 (m, 2H), 7.78−7.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.3, 30.3, 44.6, 47.1, 67.8, 69.2, 120.0, 124.9, 127.1, 127.9, 141.4, 143.3, 143.4, 157.1, 174.5; IR (cm^{-1}) 3025, 1758, 1703, 1473, 1446, 1353, 1082; HRMS *m*/*z* calcd for $C_{20}H_{19}NO_4$Na 360.1212 for (M + Na^+), found 360.1192.

1-(9*H*-Fluoren-9-ylmethyl) Hydrogen 2-Methyl-1,2-pyrrolidine Dicarboxylate (7b). Prepared as described above, using 1-bromo-3-chloropropane (166 μL, 10 equiv) in the alkylation step to provide an amorphous white solid (40.1 mg, 68% isolated yield) following purification: initial HPLC purity 92%, t_R = 11.3 min. ^{1}H NMR (CD_3OD) [mixture of two nitrogen rotamers, ratio 1.8:1][19] δ 1.40 (s, 1.1 H), 1.57 (s, 1.9H), 1.86−2.08 (m, 3H), 2.16−2.34 (m, 1H), 3.48−3.70 (m, 2H), 4.18−4.56 (m, 3H), 7.28−7.50 (m, 4H), 7.61−7.74 (m, 2H), 7.78−7.90 (m, 2H); ^{13}C NMR (CD_3OD) [mixture of two nitrogen rotamers] δ 22.3, 23.3, 23.4, 24.2, 40.5, 42.0, 48.5, 48.6, 66.6, 66.9, 68.3, 68.6, 120.9, 126.0, 126.0, 126.1, 128.1, 128.2, 128.8, 142.6, 142.6, 142.7, 142.7, 145.2, 145.5, 156.0, 156.7, 177.7; IR (cm^{-1}) 1734, 1696, 1452, 1418, 1355, 1340, 1187, 1127; HRMS *m*/*z* calcd for $C_{21}H_{21}NO_4$Na 374.1368 for (M + Na^+), found 374.1360.

1-(9*H*-Fluoren-9-ylmethyl) Hydrogen 2-Methyl-1,2-piperidine Dicarboxylate (7c). Prepared as described above, using 1-bromo-4-chlorobutane (195 μL, 10 equiv) in the alkylation step, to provide an amorphous white solid (42.3 mg, 69% isolated yield) following purification: initial HPLC purity 91%, t_R = 12.0 min. ^{1}H NMR (CD_3OD) δ 1.39 (s, 3H), 1.44−1.77 (m, 5H), 1.82−2.00 (m, 1H), 2.95−3.10 (m, 1H), 3.58−3.72 (m, 1H), 4.22 (t, *J* = 6.6 Hz, 1H), 4.33−4.45 (m, 2H), 7.20−7.42 (m, 4H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (CD_3OD) δ 19.1, 24.5, 36.1, 42.3, 48.6, 62.0, 68.5, 120.9, 126.0, 126.1, 128.2, 128.8, 142.6, 142.7, 145.2, 145.4, 157.9, 178.3; IR (cm^{-1}) 2951, 2869, 1696, 1451, 1404, 1343, 1267, 1086; HRMS *m*/*z* calcd for $C_{22}H_{24}NO_4$ 366.1705 for (M + H^+), found 366.1693.

1-(9*H*-Fluoren-9-ylmethyl) Hydrogen 2-Methylperhydro-1,2-azepine Dicarboxylate (7d). Prepared as described above, using 1,5-dibromopentane (230 μL, 10 equiv) in the alkylation step and 10% DIEA in NMP (3 mL) in the intramolecular cyclization (using a glass vessel and heating at 85 °C for 24 h with occasional agitation), to provide an amorphous white solid (46.5 mg, 73% isolated yield) following purification: initial HPLC purity 89%, t_R = 12.5 min. ^{1}H NMR (CD_3OD) [mixture of two nitrogen rotamers, ratio 3:1] δ 1.44 (s, 3H), 1.22−2.12 (m, 8H), 3.04 (dd, J_1 = 10.2 Hz, J_2 = 14.7 Hz, 0.75 H), 3.10−3.22 (m, 0.25 H), 3.68 (dd, J_1 = 5.1 Hz, J_2 = 14.5 Hz, 0.75 H), 3.84−3.96 (m, 0.25H), 4.28 (t, *J* = 5.7 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 2H), 7.28−7.48 (m, 4H), 7.58−7.76 (m, 2H), 7.83 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (CD_3OD) δ 22.9, 24.7, 30.1, 31.4, 40.4, 44.9, 48.6, 65.6, 68.4, 120.8, 126.0, 126.1, 128.1, 128.7, 142.7, 145.3, 145.5, 157.5, 177.3; IR (cm^{-1}) 2935, 1691, 1478, 1452, 1414, 1354, 1287; HRMS *m*/*z* calcd for $C_{23}H_{26}NO_4$ 380.1862 for (M + H^+), found 380.1877.

2-(9*H*-Fluoren-9-ylmethyl) Hydrogen 3-Methyl-4-hydro-1*H*-2,3-isoquinoline Dicarboxylate (7e). Prepared as described above, using α,α′-dichloro-*o*-xylene (294 mg, 10 equiv) in the alkylation step, to provide an amorphous white solid (45.1 mg, 65% isolated yield) following purification: initial HPLC purity 94%, t_R = 13.2 min. ^{1}H NMR (CD_3OD) δ 1.31 (s, 3H), 2.92 (d, *J* = 14.1 Hz, 1H), 3.21 (d, *J* = 14.1 Hz, 1H), 4.25−4.60 (m, 5H), 7.14 (broad, 1H), 7.20−7.54 (m, 8H), 7.60−7.74 (t, *J* = 7.5 Hz, 2H), 7.76−7.94 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.9, 40.4, 45.5, 47.3, 61.4, 67.5, 115.1, 119.9, 125.0, 125.8, 127.1, 127.6, 127.7, 130.0, 133.7, 134.3, 141.4, 141.4, 143.8, 144.0, 155.0, 178.6; IR (cm^{-1}) 1694, 1451, 1411, 1348, 1113, 1053; HRMS *m*/*z* calcd for $C_{26}H_{24}NO_4$ 414.1705 for (M + H^+), found 414.1697.

1-(2-Naphthalenylcarbonyl)-2-methyl-proline (7f). Prepared as described above, using 1-bromo-3-chloropropane (166 μL, 10 equiv) in the alkylation step and 2-naphthoyl chloride (320 mg, 10 equiv) instead of Fmoc-Cl during the acylation step, to provide a white solid (33.7 mg, 71% isolated yield) following purification: initial HPLC purity 89%, t_R = 8.8 min; mp 184−186 °C. ^{1}H NMR (CD_3OD) δ 1.78 (s, 3H), 1.90−2.21 (m, 3H), 2.26−2.42 (m, 1H), 3.60−3.80 (m, 2H), 7.55−7.65 (m, 3H), 7.90−8.02 (m, 3H), 8.07 (s, 1H); ^{13}C NMR (CD_3OD) δ 22.1, 25.2, 40.4, 52.5, 67.7, 124.8, 127.6, 127.9, 128.4, 128.8, 129.4, 129.6, 134.1, 135.4, 135.5, 171.5, 177.3; IR (cm^{-1}): 3004, 2986, 1737, 1715, 1635, 1624, 1472, 1418, 1184; HRMS *m*/*z* calcd for $C_{17}H_{18}NO_3$ 284.1287 for (M + H^+), found 284.1292.

1-(2-Naphthalenylcarbonyl)-2-methyl-2-piperidinecarboxylic Acid (7g). Prepared as described above, using 1-bromo-4-chlorobutane (195 μL, 10 equiv) in the alkylation step and 2-naphthoyl chloride (320 mg, 10 equiv) instead of Fmoc-Cl during the acylation step, to provide a white solid (34.4 mg, 69% isolated yield) following purification: initial HPLC purity 92%, t_R = 9.7 min; mp 189−191 °C. ^{1}H NMR (CD_3OD) δ 1.70 (s, 3H), 1.65−1.97 (m, 5H), 2.05−2.20 (m, 1H), 3.17−3.33 (m, 1H), 3.65−3.78 (m, 1H), 7.48−7.66 (m, 3H), 7.90−8.06 (m, 4H); ^{13}C NMR (CD_3OD) δ 19.0, 19.2, 24.5, 35.4, 45.6, 62.2, 124.9, 127.8, 127.9, 128.4, 128.9, 129.5, 134.2, 135.1, 135.3, 174.6, 177.7; IR (cm^{-1}) 3017, 3011, 2950, 1711, 1636, 1627, 1473, 1402, 1278, 1241, 1134; HRMS *m*/*z* calcd for $C_{18}H_{20}NO_3$ 298.1443 for (M + H^+), found 298.1414.

Manual Synthesis: Strategy 2

Preparation of the 3,4-Dichlorobenzaldehyde Imine of Ala−Wang Resin. Described previously for strategy 1 (168-μmol scale).

Alkylation of the Benzaldehyde Imine of Ala−Wang Resin with an α,ω-Dihaloalkane. Described previously for strategy 1 (168-μmol scale).

Hydrolysis of the Imine in Resin-Bound Alkylated Products. Described previously for strategy 1 (168-μmol scale).

Acylation of Resin-Bound Alkylated Product with 2-Naphthoyl Chloride. The resin-bound amine (168 μmol) was washed with NMP (4 × 4 mL, 0.5 min each). 2-Naphthoyl chloride (320 mg, 10 equiv) was dissolved in NMP (1.8 mL) and added to the resin, and the acylation was started by the addition of DIEA (570 μL, 20 equiv). The reaction mixture was rotated for 24 h. The resin was filtered and washed with NMP (6 × 4 mL, 0.5 min each), DMF (6 × 4 mL, 0.5 min each), and CH_2Cl_2 (6 × 4 mL, 0.5 min each). At this stage a small aliquot of resin was cleaved using TFA−TES (95:5) in order to determine the ratio of the acyclic naphthoyl chloro product from cleaved **8** to the cyclic naphthoyl derivative from cleaved **9**.

Intramolecular Cyclization of the Resin-Bound Alkylated Products. The resin-bound amide (168 μmol) was swollen with CH_2Cl_2 (4 × 4 mL, 0.5 min each) and NMP (4 × 4 mL, 0.5 min each). Cyclization was carried out in a glass vessel by adding tetrabutylammonium iodide (620 mg, 10 equiv) to the resin in NMP (2 mL), followed by the addition of BTPP (515 μL, 10 equiv). The reaction mixture was heated at 85 °C for 19 h with occasional agitation. The resin was then washed with NMP (6 × 4 mL, 0.5 min each), DMF (6 × 4 mL, 0.5 min each), THF (6 × 4 mL, 0.5 min each), and CH_2Cl_2 (6 × 4 mL, 0.5 min each).

Cleavage of the Product from the Resin and Final Purification. Described previously for strategy 1 (168-μmol scale).

1-(2-Naphthalenylcarbonyl)-2-methyl-proline (7f). Prepared as described above, using 1-bromo-3-chloropropane (166 μL, 10 equiv) in the alkylation step, to provide a white solid (36.6 mg, 77% isolated yield) following purification: initial HPLC purity 92%. The ratio of the acyclic naphthoyl chloro product from cleaved **8** to the cyclic naphthoyl derivative from cleaved **9** was 48:52 before cyclization in the amide stage. Analytical characterization of the product is described above for strategy 1.

1-(2-Naphthalenylcarbonyl)-2-methyl-2-piperidinecarboxylic Acid (7g). Prepared as described above, using 1-bromo-4-chlorobutane (195 μL, 10 equiv) in the alkylation step, to provide a white solid (24.5 mg, 49% isolated yield) following purification: initial HPLC purity 93%. The ratio of the acyclic naphthoyl chloro product from cleaved **8** to the cyclic naphthoyl derivative from cleaved **9** was 96:4 before cyclization in the amide stage. Analytical characterization of the product is described above for strategy 1.

Library Synthesis

Starting with eight different Fmoc-AA−Wang resins and using six different acylating agents [diversity reagents, e.g., Fmoc-Cl and 2-naphthoyl chloride] during the N-acylation step, 48 proline analogues (number of methylene groups $n = 3$) were prepared in parallel mode by strategy 1 using an Argonaut Technologies Trident Library Synthesizer (50-μmol scale). Batches of 300 μmols of each Fmoc-AA−Wang resin (Ala, Asp, Leu, Lys, Phe, Ser, Trp, and Tyr) were weighed and loaded, as isopycnic mixtures in CH_2Cl_2/DMF, into the glass reaction vessels. Fully automated procedures were then used based on the manually optimized methods described previously.

At the end of the automated syntheses, the crude cleavage products were evaporated to dryness. Aliquots of each sample of the library were analyzed by reversed-phase HPLC with the following detection systems: UV at 214 nm, ELSD and electrospray MS. Purification of the crude samples was accomplished using reversed-phase chromatography (19 × 100 mm symmetry column) and elution with a linear 10−50% gradient of 0.1% TFA of CH_3CN into 0.1% aqueous TFA at 20 mL/min for 11 min.

The ^{1}H NMR spectra of compounds **10a**−**h** include protons that show fractional integrations. These phenomena reflect slow interconversion of the cis−trans rotational isomers about the urethane C−N bond.

1-(9*H*-Fluoren-9-ylmethyl) Hydrogen 2-(4-Hydroxybenzyl)-1,2-pyrrolidine Dicarboxylate (10a). Initial HPLC purity >90%, t_R = 10.8 min; isolated yield 52%. ^{1}H NMR (CD_3OD) [mixture of two nitrogen rotamers, ratio 2:1] δ 0.86−1.14 (m, 1H), 1.44−1.74 (m, 1H), 1.90−2.25 (m, 2H), 2.58 (d, J = 14.4 Hz, 1/3 H), 2.73 (d, J = 14.4 Hz, 1/3H), 2.80−2.92 (m, 1/3H), 2.97 (d, J = 14.1 Hz, 2/3H), 2.92−3.04 (m, 2/3H), 3.38−3.54 (m, 1H), 3.62 (d, J = 14.1 Hz, 2/3H), 4.25 (t, J = 4.5 Hz, 1/3H), 4.30−4.48 (m, 4/3H), 4.54−4.66 (m, 1H), 4.96−5.05 (m, 1/3H), 6.51 (d, J = 8.4 Hz, 2/3H), 6.58 (d, J = 8.4 Hz, 2/3H), 6.70 (d, J = 8.4 Hz, 4/3H), 6.90 (d, J = 8.4 Hz, 4/3H), 7.32−7.52 (m, 4H), 7.65−7.92 (m, 4H); IR (cm^{-1}) 3026, 1713, 1695, 1614, 1515, 1452, 1419, 1357, 1343, 1196, 1173, 1137, 1106; HRMS *m*/*z* calcd for $C_{27}H_{26}NO_5$ 444.1811 for (M + H$^+$), found 444.1801.

1-(9*H*-Fluoren-9-ylmethyl) Hydrogen 2-Benzyl-1,2-pyrrolidine Dicarboxylate (10d). Initial HPLC purity >95%, t_R = 12.8 min; isolated yield 35%. ^{1}H NMR (CD_3OD) [mixture of two nitrogen rotamers, ratio 2:1] δ 0.74−1.06 (m 1H), 1.42−1.74 (m, 1H), 1.92−2.28 (m, 2H), 2.67 (d, J = 13.8 Hz, 1/3H), 2.79 (d, J = 13.8 Hz, 1/3H), 2.78−2.88 (m, 1/3H), 2.88−3.00 (m, 2/3H), 3.08 (d, J = 13.8 Hz, 2/3H), 3.35−3.52 (m, 1H), 3.72 (d, J = 13.8 Hz, 2/3H), 4.24−4.29 (m, 1/3H), 4.31−4.39 (m, 2/3H), 4.39−4.48 (m, 2/3H), 4.54−4.66 (m, 1H), 5.00−5.08 (m, 1/3H), 6.64−6.74 (m, 1H), 7.05−7.30 (m, 5H), 7.30−7.50 (m, 4H), 7.64−7.90 (m, 4H); IR (cm^{-1}) 1696, 1452, 1418, 1357, 1343, 1136; HRMS *m*/*z* calcd for $C_{27}H_{26}NO_4$ 428.1862 for (M + H$^+$), found 428.1854.

1-(9*H*-Fluoren-9-ylmethyl) Hydrogen 2-Isobutyl-1,2-pyrrolidine Dicarboxylate (10f). Initial HPLC purity >90%, t_R = 12.6 min; isolated yield 44%. ^{1}H NMR (CD_3OD) [mixture of two nitrogen rotamers, ratio 3:2] δ 0.55 (d, J = 6.0 Hz, 1.2H), 0.83 (d, J = 5.7 Hz, 1.2H), 0.88 (d, J = 6.6 Hz, 1.8 H), 1.00 (d, J = 6.6 Hz, 1.8H), 1.45−2.37 (m, 7H), 3.38−3.58 (m, 1H), 3.62−3.78 (m, 1H), 4.18 (t, J = 4.8 Hz, 0.4H), 4.28 (t, J = 6.6 Hz, 0.6H), 4.40 (d, J = 6.6 Hz, 1.2H), 4.53 (dd, J_1 = 4.8, J_2 = 10.8 Hz, 0.4H), 4.67 (dd, J_1 = 4.8, J_2 = 10.8 Hz, 0.4 H), 7.28−7.52 (m, 4H), 7.58−7.74 (m, 2H), 7.75−7.91 (m, 2H); IR (cm^{-1}) 2961, 1748, 1696, 1635, 1452, 1446, 1420, 1355, 1339, 1124; HRMS *m*/*z* calcd for $C_{24}H_{28}NO_4$ 394.2018 for (M + H$^+$), found 394.2009.

1-(9*H*-Fluoren-9-ylmethyl) Hydrogen 2-Carboxymethyl-1,2-pyrrolidine Dicarboxylate (10 g). Initial HPLC purity >90%, t_R = 9.6 min; isolated yield 42%. ^{1}H NMR (CD_3-OD) [mixture of two nitrogen rotamers, ratio 3:1] δ 1.86−2.16 (m, 2H), 2.16−2.38 (m, 1H), 2.54−2.72 (m, 1H), 2.77−2.90 (m, 1/2 H), 3.05 (d, J = 15.6 Hz, 3/4H), 3.22 (d, J = 15.6 Hz, 3/4H), 3.42−3.82 (m, 2H), 4.18−4.58 (m, 3H), 7.28−7.49 (m, 4H), 7.62−7.86 (m, 4H); IR (cm^{-1}) 3026, 1716, 1452, 1419, 1357, 1341, 1195, 1178, 1143; HRMS *m*/*z* calcd for $C_{22}H_{22}NO_6$ 396.1447 for (M + H$^+$), found 396.1435.

1-(9*H*-Fluoren-9-ylmethyl) Hydrogen 2-Methyl-1,2-pyrrolidine Dicarboxylate (10h). Initial HPLC purity >85%, t_R = 11.3 min; isolated yield 41%. Characterization as above for compound **7b**.

1-(2-Naphthalenylcarbonyl)-2-(4-hydroxybenzyl)-proline (10i). Initial HPLC purity >85%, t_R = 9.1 min; isolated yield 44%. ^{1}H NMR (CD_3OD) δ 1.38−1.54 (m, 1H), 1.78−1.98 (m, 1H), 2.12−2.30 (m, 1H), 2.32−2.48 (m, 1H), 2.92−3.05 (m, 1H), 3.08 (d, J = 13.5 Hz, 1H), 3.38−3.54 (m, 1H), 3.93 (d, J = 13.5 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 7.48−7.70 (m, 3H), 7.86−8.04 (m, 4H); IR (cm^{-1}) 3223, 2397, 1706, 1608, 1589, 1514, 1442; HRMS *m*/*z* calcd for $C_{23}H_{22}NO_4$ 376.1549 for (M + H$^+$), found 376.1547.

1-(2-Naphthalenylcarbonyl)-2-hydroxymethyl-proline (10k). Initial HPLC purity >85%, t_R = 7.3 min; isolated yield 28%. ^{1}H NMR (CD_3OD) δ 1.94−2.34 (m, 3H), 2.46−2.62 (m, 1H), 3.55−3.82 (m, 2H), 4.01 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 7.54−7.74 (m, 3H), 7.88−8.16 (m, 4H); IR (cm^{-1}) 1721, 1634, 1617, 1473, 1420, 1282, 1193; HRMS *m*/*z* calcd for $C_{17}H_{18}NO_4$ 300.1236 for (M + H$^+$), found 300.1211.

1-(2-Naphthalenylcarbonyl)-2-benzyl-proline (10l). Initial HPLC purity >90%, t_R = 11.4 min; isolated yield 28%. ^{1}H NMR ($CDCl_3$−CD_3OD) δ 1.30−1.46 (m, 1H), 1.76−1.96 (m, 1H), 2.18−2.34 (m, 2H), 2.90−3.00 (m, 1H), 3.17 (d, J = 13.8 Hz, 1H), 3.44 (ddd, J_1 = 3.0, J_2 = 7.5, J_3 = 10.4 Hz, 1H), 4.02 (d, J = 13.8 Hz, 1H), 7.25−7.44 (m, 5H), 7.48−7.60 (m, 3H), 7.80−7.94 (m, 4H); IR (cm^{-1}) 1730, 1586, 1424, 1163; HRMS *m*/*z* calcd for $C_{23}H_{22}NO_3$ 360.1600 for (M + H$^+$), found 360.1597.

1-(2-Naphthalenylcarbonyl)-2-(4-amino-butyl)-proline (10m). Initial HPLC purity >90%, t_R = 7.5 min; isolated yield 48%. ^{1}H NMR (CD_3OD) δ 1.38−1.62 (m, 1H), 1.62−1.88 (m, 3H), 1.89−2.03 (m, 1H), 2.03−2.18 (m, 2H), 2.19−2.43 (m, 2H), 2.47−2.67 (m, 1H), 3.03 (t, J = 7.5 Hz, 2H), 3.60−3.84 (m, 2H), 7.56−7.68 (m, 3H), 7.91−8.05 (m, 3H), 8.08 (s, 1H); IR (cm^{-1}) 2674, 1678, 1608, 1424, 1183, 1139; HRMS *m*/*z* calcd for $C_{20}H_{25}N_2O_3$ 341.1865 for (M + H$^+$), found 341.1858.

1-(2-Naphthalenylcarbonyl)-2-isobutyl-proline (10n). Initial HPLC purity >95%, t_R = 10.9 min; isolated yield 39%. ^{1}H NMR (CD_3OD) δ 1.10 (d, J = 6.6 Hz, 3H), 1.12 (d, J = 7.8 Hz, 3H), 1.85−2.28 (m, 5H), 2.29−2.45 (m, 1H), 2.54 (dd, J_1 = 6.6, J_2 = 14.7 Hz, 1H), 3.62−3.74 (m, 1H), 3.74−3.90 (m, 1H), 7.52−7.68 (m, 3H), 7.88−8.03 (m, 3H), 8.05 (s, 1H); IR (cm^{-1}) 1734, 1559, 1419, 1188, 1133; HRMS *m*/*z* calcd for $C_{20}H_{24}NO_3$ 326.1756 for (M + H$^+$), found 326.1745.

1-(2-Naphthalenylcarbonyl)-2-carboxymethyl-proline (10o). Initial HPLC purity >90%, t_R = 7.4 min; isolated yield 39%. ^{1}H NMR (CD_3OD) δ 1.88−2.24 (m, 2H), 2.32 (ddd, J_1 = 2.7, J_2 = 6.9, J_3 = 13.2 Hz, 1H), 2.58−2.76 (m, 1H), 3.14 (d, J = 15.6 Hz, 1H), 3.57 (d, J = 15.6 Hz, 1H), 3.56−3.66 (m, 1H), 3.75−3.90 (m, 1H), 7.52−7.68 (m, 3H), 7.90−8.04 (m, 3H), 8.06 (s, 1H); IR (cm^{-1}) 1717, 1617, 1479, 1419, 1191; HRMS *m*/*z* calcd for $C_{18}H_{17}NO_5Na$ 350.1004 for (M + H$^+$), found 350.0994.

1-(2-Naphthalenylcarbonyl)-2-methyl-proline (10p). Initial HPLC purity >90%, t_R = 8.8 min; isolated yield 45%. Characterization as above for compound **7f**.

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Supporting Information Available. Proton NMR spectra of all products. This material is available free of charge via the Internet at htpp://pubs.acs.org.

References and Notes

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(10) The following abbreviations are used: BTPP, *tert*-butylimino-tri(pyrrolidino)phosphorane; DIEA, *N*,*N*-diisopropylethylamine; FAB-MS, fast atom bombardment mass spectrometry; Fmoc, 9-fluorenylmethoxycarbonyl; Fmoc-Cl, 9-fluorenylmethyl chloroformate; HOAc, acetic acid; UPS, unnatural peptide synthesis; TES, triethylsilane; TMOF, trimethyl orthoformate.

(11) For example, the presence of cross-linked side products was minimized during the alkylation by using a 10-fold excess of α-bromo-*ω*-chloroalkanes. In another example of a side reaction, when $n = 3$, there was evidence that the *ω*-bromo compound led to partial olefin formation by elimination.

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(15) Early experiments involved use of α,α′-dibromo-*o*-xylene as the alkylating agent, which led to considerably lower crude HPLC purities and yields.

(16) For $n = 2$ with strategy 2, the desired four-membered ring was not obtained; neither was N-acylated chloro-substituted starting material **8** recovered. We believe there is a competing intramolecular cyclization by O-alkylation from **8** to generate a six-membered imidate.

(17) A cleavage mixture of TFA−TES (95:5) is preferred over TFA−H_2O (95:5) in order to minimize partial decomposition of the N-acylated final products over time. Unacylated material resulting from the acid-catalyzed hydrolysis can be inferred by the presence of 2-naphthoic acid in the HPLC of the crude products.

(18) Reverse *O*- to *N*-acyl migration can be accomplished by allowing the *O*-acyl product to stand in acetonitrile in the presence of DIEA overnight to complete the conversion to the *N*-acyl desired product. For a report of a similar *O*- to *N*-acyl migration under basic conditions, see: Owens, T. D.; Semple, J. E. *Org. Lett.* **2001**, *3*, 3301−3304.

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