Solid-Phase Synthesis of Benzopiperazinones

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Received September 9, 1997

This article describes an efficient method for the solid phase synthesis of benzopiperazinones (1,2,3,4-tetrahydroquinoxalin-2-ones) with four independently variable functional groups. Commercially available 4-fluoro-3-nitrobenzoic acid (FNBA) was anchored directly to Wang resin and to amino acid-containing Wang resin. Treatment of these resins with amino acid derivatives afforded enantiomerically pure aniline intermediates via an ipso-fluoro displacement in high yields. Reduction of the aromatic nitro group with aqueous 2 M $SnCl_2$, followed by spontaneous intramolecular cyclization, afforded benzopiperazinones in good yields. Complete acylation of the aniline site (**N4**) was achieved using several chloro- or thiochloroformates and $NaHCO_3$ in anhyd THF/DMF at 80 °C under an argon atmosphere. Alkylation of the anilide nitrogen (**N1**) with lithiated (*S*)-(−)-4-benzyl-2-oxazolidinone and benzyl bromide afforded alkylated benzopiperazinones in good yields with a high enantiomeric excess (>95% ee). A number of side reactions including racemization were discovered in our studies and are addressed.

Introduction

The use of solid-phase synthesis to deliver vast numbers of linear oligomers, such as peptides and oligonucleotides, has been the focus of research interests over the past several years.[1] The development of chemistries amenable to the solid-phase synthesis of small molecule heterocycles is now receiving increased attention owing to the desire to synthesize libraries containing nonpeptidic molecules.[2] The benzopiperazinone (1,2,3,4-tetrahydroquinoxalin-2-one) ring system is structurally related to the widely employed benzodiazepine nucleus and yet has been less widely used in drug discovery. Examples of biologically active benzopiperazinones include inhibitors of aldose reductase,[3] partial agonists of the γ-aminobutyric acid (GABA)/benzodiazepine receptor complex,[4] and angiotensin II receptor antagonists.[5] Also, two patents have described the synthesis of 4-(acyloxy)benzopiperazinone derivatives with antiviral activity, as associated with HIV.[6] In this manuscript we describe a novel solid-phase synthetic route for the preparation of libraries of benzopiperazinones exploiting four sites for chemical diversity (Figure 1).

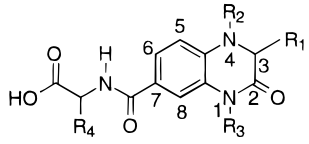

Figure 1.

While this manuscript was in preparation, a paper appeared on the solid-phase synthesis of benzopiperazinones,[7] which employed a very similar route for the synthesis of the heterocyclic ring system. However, the substituents were varied at only two centers (N4 and C3), and the chemical nature of the substituents introduced at N4 were different from those in the present manuscript. In particular, only alkyl groups were incorporated at N4 and C3. Also, the present manuscript describes a number of side reactions, including racemization at the C3 carbon, that were not discussed in the previous publication. Methods to avoid these problems are discussed.

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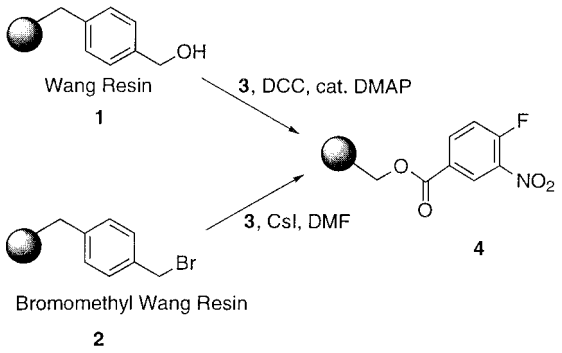
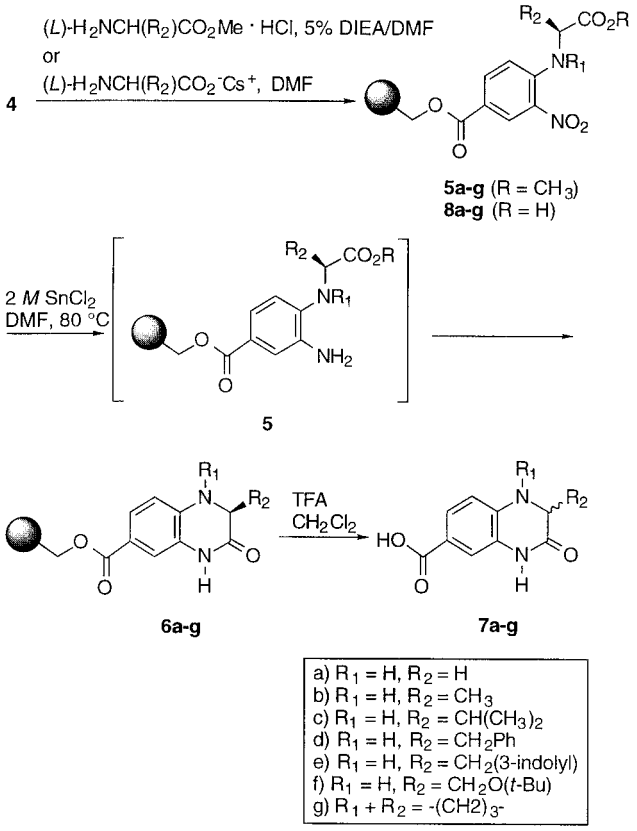
S0022-3263(97)01688-5 CCC: $15.00
Published on Web 01/30/1998

Scheme 1



Scheme 2



Results and Discussion

Construction of Benzopiperazinone Framework and Introduction of Diversity at C3. Our synthesis is similar to the solution phase route of TenBrink[4] et al. and begins with the incorporation of 4-fluoro-3-nitrobenzoic acid (**3**) (FNBA) onto the TFA-labile Wang resin **1** via an ester linkage. We first attempted to anchor **3** to Wang resin using standard peptide coupling reagents such as *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and *N*,*N*-diisopropylethylamine (DIEA) in *N*,*N*-dimethylformamide (DMF); however, this approach led to substantial quantities of a side product arising from ipso-fluoride displacement by the hydroxyl unit of 1-hydroxybenzotriazole. Thus, although previous workers have used *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) as a coupling reagent in the synthesis of benzopiperazinones, we found that HBTU did not afford any of the desired material. Resin-bound 4-fluoro-3-nitrocarboxylate **4** was successfully prepared by either coupling **3** to **1** in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in dichloromethane (DCM), or by coupling **3** to bromomethyl Wang resin[8] **2** using CsI in DMF (Scheme 1).

The subsequent ipso-fluoride displacement with amino acid esters proceeded uneventfully delivering 3-nitro-4-aniline benzoates **5** under mild conditions (Scheme 2).[9] To monitor the progress of the fluoride displacement, aliquots of resin (approximately 20 mg) were removed from the reaction mixture, filtered, washed with DMF, isopropyl alcohol (IPA), and $CDCl_3$, and dried. The resin was then treated with a 1:1 mixture of CD_2Cl_2/TFA-*d* for approximately 30 min at rt, filtered, and analyzed by ^{1}H NMR.

Our first attempt to reduce the aromatic nitro group utilized conditions recently reported by Pavia and Goff using an aqueous 2 M $SnCl_2$ solution in DMF at 25 °C.[10] As a model reaction, we anchored *o*- and *p*-nitro benzoic acids to Wang resin and treated the resulting resins with 10 equiv of 2 M $SnCl_2$ in DMF at rt overnight to obtain the desired aniline derivatives. However, the reduction of resin bound nitro esters **5** was incomplete under these reaction conditions, even after 4 days of treatment with $SnCl_2$. While this problem might be alleviated by using more costly Tentagel or Argogel resins, we instead searched for conditions that could be carried out reproducibly on Wang resin. After evaluating several reducing reagents ($SnCl_2$, Na_2S, $Na_2S_2O_4$) and reaction conditions, the aromatic nitro group could be fully reduced with aqueous 2 M $SnCl_2$ solution in DMF at 80 °C under an argon atmosphere.[11] The resulting anilines cyclized to afford **6** without any trace of **5** or uncyclized material as determined by ^{1}H NMR analysis of the cleaved material **7** (Scheme 2).

Chiral HPLC analysis of **7b** indicated that it had partially racemized, affording a material with a 50% ee. To determine if the racemization occurred during either the ipso fluoride displacement, nitro reduction, or TFA cleavage, the nitro intermediate **5b** was cleaved from the resin and determined to be optically pure by chiral HPLC (99% ee). To ascertain if the preservation of the optical purity of **5b** is general, the optical purity of a sampling of the nitro intermediates **5** was determined (Table 1).

Chiral HPLC Analysis Conditions For 5b, 5d, 5f and 5g. We next considered the possibility that the racemization might occur by direct enolization of the methyl ester intermediate **5b**−**g** during the nitro reduction step. To test this possibility, we introduced the amino acid residue as a free acid rather than as the methyl ester, providing the free acid intermediates **8a**−**g** (Scheme 2). Treatment of **4** with amino acid cesium salts delivered **8a**−**g** which were then reduced in the same manner as described previously to afford **6a**−**g**.

(8) Mergler, M.; Nyfeler, R.; Gosteli, J. *Tetrahedron Lett.* **1989**, *30*, 6741.

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(11) Presence of oxygen during the reduction step also produced quantitites of 3,4-dihydro-2(1*H*)-quinoxalinones.

Table 1

compound	column	wavelength (nm)	solvents	flow rate (mL/min)	ee (%)
5b	Chiralcel OD	250	80% Hexane, 20% EtOH, 0.1% MeOH, 0.1% TFA	1.0	**99**
5d	Chiralcel OD	280	94% MeOH, 6% H_2O, 0.1% TFA	0.6	**99**
5f	Chiralcel OJ	250	75% CO_2, 25% CH_3CN, 0.1% TFA	2.0	>**97**
5g	Chiralcel OD	280	95% MeOH, 6% H_2O, 0.1% TFA	0.5	**100**

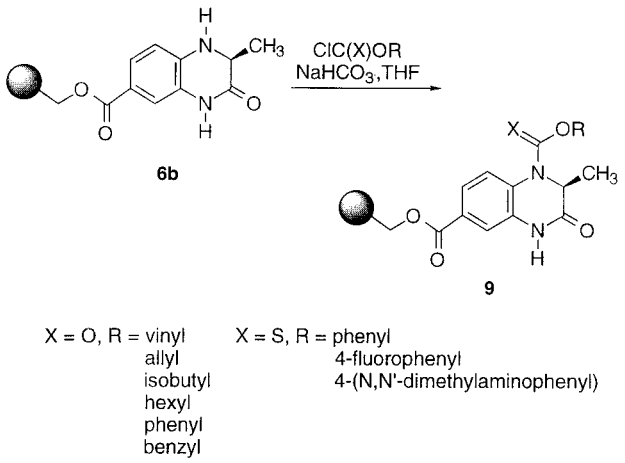
Treatment of **6a**−**g** with a 50% CH_2Cl_2/TFA mixture for 2 h released the desired benzopiperazinones **7**. Unfortunately, the chiral purity and yield of the benzopiperazinones obtained with this method were frequently poor and side-chain dependent. This finding suggests that the loss of chirality in compounds **6** is caused by TFA during the cleavage process. To determine if lactam formation occurs spontaneously during the reduction step and not during TFA cleavage, the infrared spectrum of the resin-bound material **8**, after the $SnCl_2$ reduction, was obtained by IR-ATR (attenuated total reflectance) on multiple beads.[9c, 12] The resin bound material was then treated with DCC in THF at rt, and then analyzed again by IR-ATR. We found that the infrared spectra for the immobilized material before and after DCC treatment were identical, which suggests that the amine intermediate obtained upon reduction of **8** rapidly cyclizes under the reduction conditions to give **6**.

Thus, the use of amino acid cesium salts in place of methyl esters failed to lead to any improvement in yield or enantiomeric purity. We prefer to use amino acid esters because of their better solubility in organic solvents. Also, the methyl ester unit provides a characteristic singlet in the ^1H NMR spectrum that serves as a convenient reference to monitor the reduction/cyclization process. Although the racemization was initially considered a problem, we soon found that the introduction of substitutents at the N4 position suppressed this reaction entirely.

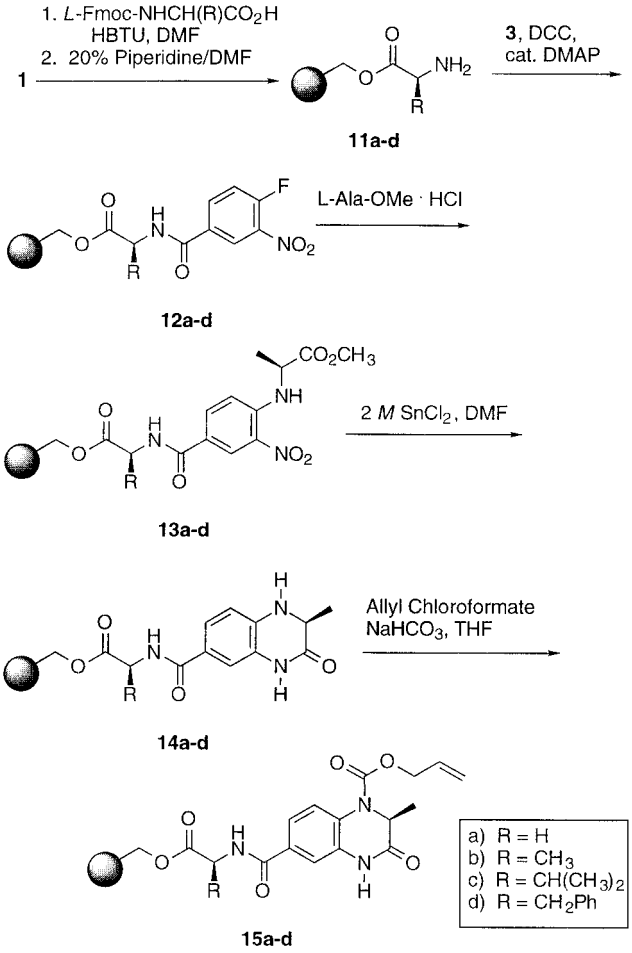
Introduction of Substituents at N4. With a reproducible route to **6** in hand, the functionalization of the secondary aniline and the anilide was then investigated using **6b** as a representative example. We examined the conversion of the anilino site to the corresponding urethane, because this modification of the heterocycle had previously been reported to provide a compound with antiviral activity.[6] Indeed, the aniline site could be reproducibly acylated with chloroformates and thiochloroformates at 80 °C under an argon atmosphere (Scheme 3).

A major added advantage of acylation of the N4 position is that this modification greatly decreased the extent of racemization during the acid cleavage. For instance, **9** (X = O, R = allyl) derived from L-alanine afforded material with an ee of 99%. This finding serves to further confirm that racemization occurred during acidolytic cleavage of **6**. To increase the number of points for chemical diversity in the benzopiperazinones scaffold, different amino acids were used as linkers between the aromatic carboxylic acid unit of the scaffold and the solid support. This approach involved anchoring Fmoc-protected amino acids to **1** via an ester linkage, deprotection of the terminal amino group with a 20% piperidine solution in DMF, and coupling **3** to **11** through an amide linkage to afford **12**. As representative examples, ipso-fluoride displacement of **12** with L-alanine methyl ester

Scheme 3



Scheme 4



hydrochloride followed by nitro reduction/cyclization and aniline acylation with allyl chloroformate provided **15** in 17% to 50% overall isolated yields (Scheme 4).

Introduction of Substituents at N1. Functionalization of the anilide site **N1** was investigated next using

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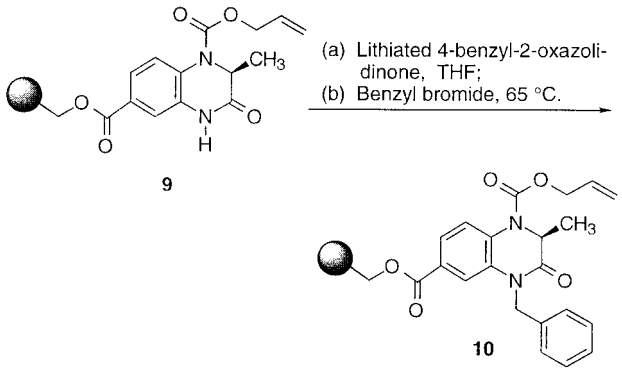
Scheme 5



lithiated 4-benzyl-2-oxazolidinone[13] and benzyl bromide to produce **10** with an ee > 99% (Scheme 5). Satisfactory yields were obtained in anhyd THF at 60−65 °C under an argon atmosphere with vortexing for 48 h to avoid decomposition of the polymer support.

Conclusions

This manuscript, together with a previous publication,[7] describe general approaches to the solid phase synthesis of the benzopiperazinone ring system. The solid phase synthesis of these compounds is relatively straightforward, although the oxidation of the ring system proved to be problematic for compounds that are not substituted at the anilino nitrogen.[11] This side reaction was previously reported Lee et al.,[7] who showed that it can be eliminated by addition of an alkyl group to the anilino nitrogen. We find that N4 acyl groups are also effective in suppressing this side reaction. A second major problem, not previously reported by Lee et al., was partial racemization at the C3 carbon of the heterocycle. This process appears to be catalyzed by TFA during cleavage of the benzopiperazinones from the resin. Fortunately, acylation of the anilino nitrogen results in a very substantial decrease in the extent of the racemization. It is currently unclear whether the addition of an alkyl group would have a similar effect on this side reaction.

Benzopiperazinones should provide a system of considerable potential for the introduction of chemical diversity. This scaffold provides four sites for incorporation of diversity elements: (1) Different functional groups may be inserted at C7 of the aryl ring, depending on the linkage of the aromatic unit of the scaffold to the solid support. (2) Miscellaneous α-amino esters may be used for the ipso-fluoro displacement. (3) Different acylating agents may be used to provide diverse substituents at the aniline nitrogen N4. (4) Suitable electrophiles for the alkylation of the acetanilide nitrogen provide diversity at N1. In addition, the recent manuscript of Lee et al. describes the use of alkyl halides to introduce alkyl groups at the aniline nitrogen atom. Thus, benzopiperazinones should provide a versatile scaffolding for synthesis of chemical libraries.

Experimental Section

General The ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. The chemical shifts are reported in ppm (δ) relative to TMS in the solvent listed. Low and high-resolution mass spectra were recorded with the electrospray ionization technique. All starting materials were purchased from commercial sources and used as received without further purification. Wang resin was obtained from Advanced ChemTech. All resins were dried by passing air through them for 20−30 min. Room-temperature reactions containing up to 200 mg of resin were performed in bottom-and-top capped polypropylene-fritted tubes (parts: QS−B, QS-T, and QS-Q, respectively) manufactured by Mitchell's Plastics (130 31st Street/Northwest, Norton, OH 44203; phone number: (800) 457−6862) and purchased from VWR. Oxygen-free water and DMF were prepared by bubbling dispersed argon into them for 1 h. Oxygen-free water was used to make oxygen-free aqueous 2 M $SnCl_2$ solutions. The polypropylene-fritted tubes were shaken using a tube rotator/rocker (part: 56264-302) purchased from VWR. Reactions at 75−80 °C containing up to 200 mg of resin were performed in screw-capped Kimax culture tubes (13 mm × 100 mm) (part: 60828−208) purchased from VWR. The screw-capped Kimax culture tubes were placed in Modular Heating Blocks and heated using a Dry Block Heater (both items acquired from VWR). The screw-capped Kimax culture tubes were shaken by placing the Dry Block Heater on a Rotomix Orbital Mixer (part: 58922−614), which was also purchased from VWR. Scaled-up reactions (>500 mg) were performed in round-bottomed flasks shaken on a Rotomix Orbital Mixer.

To obtain the spectrometric data reported herein resin-bound compounds were first treated with a 50% TFA/DCM solution for 2 h at rt. The suspension was filtered, and the resin was washed with DCM (3 × 2 mL). The filtrates were combined and evaporated under reduced pressure. The residue was then taken up in a 50% acetonitrile:water solution and freeze-dried overnight. The resulting residue was then taken in a minimum volume of a 50% acetonitrile:water solution, purified via preparative reverse-phase HPLC, and freeze-dried overnight.

Procedure for Preparation of Resin 4. A 1-L single-necked round-bottomed flask was charged with Wang resin (50.0 g, 36.5 mmol, 0.73 mmol/g loading), DMF (500 mL), triphenylphospine (47.9 g, 5 equiv), and carbon tetrabromide (60.5 g, 5 equiv). The flask was shaken for 2.5 h at rt, and the resin was then filtered, washed thoroughly (300 mL volumes) with DMF (2×), DCM (2×), IPA (2×), DMF (2×), DCM (2×), and IPA (2×), and dried by passing air through the resin. This resin was then suspended in DMF and reacted with 4-fluoro-3-nitrobenzoic acid (13.5 g, 2 equiv), cesium iodide (18.96 g, 2 equiv), and DIEA (9.43 g, 2 equiv)at rt overnight. The final yellow resin was filtered, washed thoroughly (300-mL volumes) with water (2×), DMF (2×), DCM (2×), IPA (2×), water (2×), DMF (2×), DCM (2×), and IPA (2×), and dried first by passing air through it and then in an oven (70 °C) under reduced pressure overnight to afford a resin with a theoretical loading of 0.698 mmol/g. The manufacturers' reported loading of the Wang resin was used in the calculation of the theoretical yields of the final products.

Procedure for Preparation of Resins 5 and 13. A 50-mL round-bottomed single-necked flask was charged with either resin **4** or **12**, the amino ester hydrochloride salts (2 equiv), and 5% DIEA/DMF. The mixture was agitated at rt for 24 h, filtered, washed with DMF (3×), DCM (3×), and IPA (3×) in that order twice, and dried. Chiral HPLC conditions for ee determination of compounds **5b**, **5d**, **5f**, and **5g** are given in Table 1.

4-{[(1*S*)-1-(Methyloxycarbonyl)ethyl]amino}-3-nitrobenzoic acid (**5b**) (72% yield from **1**, theoretical loading of 0.617 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 12.98 (brs, 1H), 8.64 (s, 1H), 8.61 (s, 1H), 7.99 (dd, J = 9.2, 1.8 Hz, 1H), 7.10 (d, J = 9.2 Hz, 1H), 4.78−4.69 (m, 1H), 3.74 (s, 3H), 1.52 (d, J = 7.0 Hz, 3H); ^{13}C NMR [$(CD_3)_2SO$]: δ 172.9, 166.2, 146.3, 136.6, 131.5, 128.8, 118.6, 115.4, 53.0, 51.0, 18.3; mass spectrum (ESIMS), m/z 269 [$(M + H)^+$]. HRMS: Calcd mass 269.077361; found 269.077069. Anal. Calcd for $C_{11}H_{12}N_2O_6 \cdot 0.25\ H_2O$: C, 48.45; H, 4.62; N, 10.27. Found: C, 48.34; H, 4.39; N, 9.94.

2-[(4-{[(1*S*)-1-(Methyloxycarbonyl)ethyl]amino}-3-nitrophenyl)carboxamido]acetic acid (**13a**) (64% yield from **1**, theoretical loading of 0.596 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 8.91 (t,

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J = 5.7 Hz, 1H), 8.66 (d, J = 2.2 Hz, 1H), 8.49 (d, J = 7.3 Hz, 1H), 7.99 (dd, J = 8.8, 1.8 Hz, 1H), 7.07 (d, J = 9.2 Hz, 1H), 4.74−4.65 (m, 1H), 3.87 (d, J = 5.9 Hz, 2H), 3.69 (s, 3H), 1.47 (d, J = 7.0 Hz, 3H); ^{13}C NMR [$(CD_3)_2SO$]: δ 172.3, 171.7, 164.9, 145.5, 135.2, 131.5, 126.5, 121.7, 115.2, 53.0, 50.9, 41.6, 18.3; mass spectrum (ESIMS), m/z 326 [$(M + H)^+$]. HRMS [$(M + H)^+$]: Calcd mass 326.098825; found 326.097630.

Procedure for Preparation of Resin 8. Amino acids (10 equiv) were dissolved in a minimum volume of a 2 M aqueous Cs_2CO_3 solution at rt followed by removal of water under reduced pressure. Resin **1** (100 mg) and anhydrous DMF (10 mL) were immediately added to the dry cesium salt. The vessel was sealed and shaken at rt for 24 h. The final orange resin was filtered, washed thoroughly (1.5−2.0 mL volumes) with water (3×), DMF (3×), IPA (3×), water (3×), DMF (3×), and IPA (3×), and dried.

Procedure for Preparation of Resin 6. A screw-capped Kimax culture tube was charged with **5** (150 mg), oxygen-free 2 M $SnCl_2$ (20 equiv), and oxygen-free DMF (1.5 mL). The tube was purged with argon for 1 min, screw-capped, and placed in a preheated heating block (80 °C). The reaction was horizontally agitated overnight. The culture tube was allowed to cool to rt, the resin was then filtered into a polypropylene-fritted tube and washed thoroughly (1.5−2.0 mL volumes) with water (3×), IPA (3×), DCM (3×), IPA (3×), and $CHCl_3$ (3×), and dried. Chiral HPLC analysis of **7b** was performed at 280 nm using a Chiralcel OG column and 80% hexanes, 20% EtOH, and 0.1% TFA as eluent with a flow rate of 1.5 mL/min at rt.

Procedure for Preparation of Resin 9 and 15. A screw-capped Kimax culture tube was charged with either resin **6** or **14** (150 mg), $NaHCO_3$ (10 equiv), anhyd THF (1.5 mL), and chloro- or thiochloroformate (10 equiv). The tube was purged with argon for 1 min, screw-capped, and placed in a preheated heating block (80 °C). The reaction was horizontally agitated overnight. The culture tube was allowed to cool to rt, and the resin was then filtered into a polypropylene-fritted tube and washed thoroughly (1.5−2.0 mL volumes) with water (3×), IPA (3×), DCM (3×), IPA (3×), $CHCl_3$ (3×), and dried.

(3*S*)-4-*N*-(Vinyloxycarbonyl)-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one [9 (X = O, R = vinyl)] (52% yield from **5b**, theoretical loading of 0.614 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 10.87 (s, 1H), 7.66−7.55 (m, 3H), 7.12 (dd, J = 13.9, 6.2 Hz, 1H), 4.92−4.79 (m, 2H), 4.63 (dd, J = 6.2, 1.8 Hz, 1H), 1.12 (d, J = 7.3 Hz, 3H); ^{13}C NMR [$(CD_3)_2SO$]: δ 168.5, 166.9, 150.4, 142.5, 130.8, 128.3, 127.2, 124.6, 124.0, 117.3, 98.5, 53.3, 16.2; mass spectrum (ESIMS), m/z 277 [$(M + H)^+$]. HRMS [$(M + H)^+$]: Calcd mass 277.082447; found 277.081522. Anal. Calcd for $C_{13}H_{12}N_2O_5 \cdot 0.4C_2HF_3O_2$: C, 51.50; H, 3.88; N, 8.70. Found: C, 51.86; H, 4.18; N, 8.94.

(3*S*)-4-*N*-(Allyloxycarbonyl)-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one [9 (X = O, R = allyl)] (69% yield from **5b,** theoretical loading of 0.609 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 10.86 (s, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.58−7.55 (m, 3H), 6.02−5.89 (m, 1H), 5.32−5.19 (m, 2H), 4.87−4.80 (m, 1H), 4.72−4.61 (m, 2H), 1.11 (d, J = 7.3 Hz, 3H); ^{13}C NMR [$(CD_3)_2$-SO]: δ 168.7, 166.9, 152.7, 132.9, 130.5, 127.9, 127.8, 124.3, 123.9, 118.5, 117.2, 67.1, 53.2, 16.2; mass spectrum (ESIMS), m/z 291 [$(M + H)^+$]. HRMS [$(M + H)^+$]: Calcd mass 291.098097; found 291.098443. Anal. Calcd for $C_{14}H_{14}N_2O_5 \cdot 0.6H_2O$: C, 55.85; H, 5.09; N, 9.30. Found: C, 55.68; H, 4.73; N, 8.99. Chiral HPLC analysis was performed at 250 nm using a Chiralcel OD column and 80% hexanes, 20% IPA, and 0.1% TFA as eluents at a flow rate of 0.9 mL/min at rt.

(3*S*)-4-*N*-(Isobutyloxycarbonyl)-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one [9 (X = O, R = isobutyl)] (64% yield from **5b**, theoretical loading of 0.602 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 10.85 (s, 1H), 7.67−7.64 (m, 1H), 7.58−7.55 (m, 2H), 4.86−4.79 (m, 1H), 3.98−3.88 (m, 2H), 1.96−1.85 (m, 1H), 1.11 (d, J = 7.0 Hz, 3H), 0.87 (dd, J = 6.8, 0.9 Hz, 6H); ^{13}C NMR [$(CD_3)_2SO$]: δ 168.7, 166.9, 153.0, 130.4, 128.0, 127.7, 124.3, 123.9, 117.2, 72.6, 53.1, 27.7, 19.3, 16.3; mass spectrum (ESIMS), m/z 307 [$(M + H)^+$]. HRMS [$(M)^+$]: Calcd mass 306.121572; found 306.120150. Anal. Calcd for $C_{15}H_{18}N_2O_5 \cdot 0.5H_2O$: C, 57.14; H, 6.07; N, 8.88. Found: C, 57.52; H, 5.78; N, 8.60.

(3*S*)-4-*N*-(*n*-Hexyloxycarbonyl)-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one [9 (X = O, R = *n*-hexyl)] (57% yield from **5b**, theoretical loading of 0.592 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 12.92 (brs, 1H), 10.85 (s, 1H), 7.67−7.64 (m, 1H), 7.57−7.54 (m, 2H), 4.85−4.78 (m, 1H), 4.19−4.10 (m, 2H), 1.61−1.55 (m, 2H), 1.31−1.23 (m, 6H), 1.10 (d, J = 7.3 Hz, 3H), 0.83−0.79 (m, 3H); ^{13}C NMR [$(CD_3)_2SO$]: δ 168.8, 166.9, 153.0, 130.4, 128.0, 127.6, 124.3, 123.9, 117.2, 66.9, 53.1, 31.2, 28.4, 25.5, 22.4, 16.3, 14.2; mass spectrum (ESIMS), m/z 335 [$(M + H)^+$]. HRMS [$(M)^+$]: Calcd mass 334.152872; found 334.151961. Anal. Calcd for $C_{17}H_{22}N_2O_5 \cdot 0.2H_2O$: C, 60.26; H, 6.69; N, 8.27. Found: C, 59.87; H, 6.59; N, 8.08.

(3*S*)-4-*N*-(Phenyloxycarbonyl)-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one [9 (X = O, R = phenyl)] (34% yield from **5b**, theoretical loading of 0.595 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 12.97 (brs, 1H), 10.94 (s, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 5.5 Hz, 2H), 7.40 (t, J = 7.9 Hz, 2H), 7.29−7.22 (m, 3H), 4.97−4.91 (m, 1H), 1.21 (d, J = 7.3 Hz, 3H); ^{13}C NMR [$(CD_3)_2SO$]: δ 168.7, 166.9, 151.6, 151.0, 130.8, 129.8, 128.2, 127.6, 126.4, 124.6, 124.0, 122.3, 117.3, 53.7, 16.3; mass spectrum (ESIMS), m/z 327 [$(M + H)^+$]. HRMS [$(M)^+$]: Calcd mass 326.090272; found 326.089544. Anal. Calcd for $C_{17}H_{14}N_2O_5 \cdot H_2O$: C, 59.30; H, 4.68; N, 8.14. Found: C, 58.89; H, 4.27; N, 7.76.

(3*S*)-4-*N*-(Benzyloxycarbonyl)-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one [9 (X = O, R = benzyl)] (55% yield from **5b**, theoretical loading of 0.590 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 10.94 (1H, s), 7.68 (d, J = 4.4 Hz, 1H), 7.56−7.53 (m, 2H), 7.40−7.29 (m, 5H), 5.21 (s, 2H), 4.88−4.81 (m, 1H), 1.11 (d, J = 7.3 Hz, 3H); ^{13}C NMR [$(CD_3)_2SO$]: δ 168.7, 166.9, 152.9, 136.2, 130.5, 129.0, 128.6, 128.4, 127.9, 127.8, 124.3, 123.9, 117.2, 68.2, 53.2, 16.3; mass spectrum (ESIMS), m/z 341 [$(M + H)^+$]. HRMS [$(M + H)^+$]: Calcd mass 341.113747; found 341.112325. Anal. Calcd for $C_{18}H_{16}N_2O_5 \cdot 0.5H_2O$: C, 61.86; H, 4.91; N, 8.01. Found: C, 61.83; H, 4.69; H, 7.66.

2-{[(2*S*)-1-(Allyloxycarbonyl)-2-methyl-3-oxo-1,2,3,4-tetrahydro-6-quinoxalinyl]carboxamido}acetic acid (15a) (17% yield from **1**, theoretical loading of 0.589 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 10.86 (s, 1H), 8.79 (t, J = 5.7 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.51−7.46 (m, 2H), 6.02−5.90 (m, 1H), 5.32−5.19 (m, 2H), 4.86−4.79 (m, 1H), 4.70−4.62 (m, 2H), 3.88−3.86 (m, 2H), 1.11 (d, J = 7.3 Hz, 3H); ^{13}C NMR [$(CD_3)_2$-SO]: δ 171.6, 168.8, 166.1, 153.0, 133.0, 131.3, 130.6, 126.6, 124.2, 121.3, 118.5, 115.8, 67.1, 53.1, 41.7, 16.1; mass spectrum (ESIMS), m/z 346 [$(M - H)^-$]. HRMS [$(M + H)^+$]: Calcd mass 348.119561; found 348.120224. Anal. Calcd for $C_{16}H_{17}N_3O_6 \cdot 0.5C_2HF_3O_2$: C, 50.50; H, 4.36; N, 10.39. Found: C, 50.71; H, 4.42; N, 10.54.

(2*S*)-2-{[(2*S*)-1-(Allyloxycarbonyl)-2-methyl-3-oxo-1,2,3,4-tetrahydro-6-quinoxalinyl]carboxamido}propanoic acid (15b) (32% yield from **1**, theoretical loading of 0.584 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 10.83 (s, 1H), 8.63 (d, J = 7.3 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.52 (dd, J = 8.4, 1.8 Hz, 1H), 7.44 (s, 1H), 6.02−5.90 (m, 1H), 5.32−5.19 (m, 2H), 4.86−4.79 (m, 1H), 4.72−4.60 (m, 2H), 4.39−4.30 (m, 1H), 1.34 (d, J = 7.3 Hz, 3H), 1.10 (d, J = 7.3 Hz, 3H); ^{13}C NMR [$(CD_3)_2SO$]: δ 174.5, 168.8, 165.9, 152.8, 133.0, 131.4, 130.5, 126.5, 124.1, 121.7, 118.5, 115.9, 67.1, 53.1, 48.6, 17.3, 16.1; mass spectrum (ESIMS), m/z 360 [$(M - H)^-$]. HRMS [$(M + H)^+$]: Calcd mass 362.135211; found 362.133964. Anal. Calcd for $C_{17}H_{19}N_3O_6 \cdot 0.3C_2HF_3O_2$: C, 53.44; H, 4.92; N, 10.62. Found: C, 53.48; H, 4.86; N, 10.62.

(2*S*)-2-{[(2*S*)-1-(Allyloxycarbonyl)-2-methyl-3-oxo-1,2,3,4-tetrahydro-6-quinoxalinyl]carboxamido}-3-methylbutanoic acid (15c) (50% yield from **1**, theoretical loading of 0.574 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 10.82 (1H, s), 8.39 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.54 (dd, J = 8.4, 1.8 Hz, 1H), 7.43 (d, J = 1.5 Hz, 1H), 6.02−5.90 (m, 1H), 5.33−5.19 (m, 2H), 4.87−4.80 (m, 1H), 4.72−4.60 (m, 2H), 4.24−4.19 (m, 1H), 2.20−2.09 (m, 1H), 1.11 (d, J = 7.3 Hz, 3H), 0.93 (t, J = 6.6 Hz, 6H); ^{13}C NMR [$(CD_3)_2SO$]: δ 173.4, 168.8, 166.6, 152.8, 133.0, 131.6, 130.4, 126.5, 124.0, 122.0, 118.5, 116.1, 67.1, 58.8, 53.1, 29.9, 19.7, 19.2, 16.1; mass spectrum (ESIMS),

m/*z* 388 [(M − H)$^-$]. HRMS [(M + H)$^+$]: Calcd mass 390.166511; found 390.165683.

(2*S*)-2-{[(2*S*)-1-(Allyloxycarbonyl)-2-methyl-3-oxo-1,2,3,4-tetrahydro-6-quinoxalinyl]carboxamido}-3-phenylpropanoic acid (**15d**) (49% yield from **1**, theoretical loading of 0.559 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 10.85 (s, 1H), 8.68 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 9.9, 1.8 Hz, 1H), 7.41 (d, J = 1.8 Hz, 1H), 7.37−7.21 (m, 4H), 7.17−7.12 (m, 1H), 6.02−5.89 (m, 1H), 5.32−5.19 (m, 2H), 4.85−4.78 (m, 1H), 4.72−4.60 (m, 2H), 4.59−4.50 (m, 1H), 3.15 (dd, J = 13.8, 4.2 Hz, 1H), 3.05−2.97 (m, 1H), 1.09 (d, J = 7.3 Hz, 3H); ^{13}C NMR [$(CD_3)_2SO$]: δ 173.5, 168.8, 166.0, 152.8, 138.9, 133.0, 131.3, 130.5, 129.5, 128.6, 126.8, 126.5, 124.1, 121.6, 118.5, 115.9, 67.1, 54.7, 53.1, 36.7, 16.1; mass spectrum (ESIMS), *m*/*z* 436 [(M − H)$^-$]. HRMS [(M + H)$^+$]: Calcd mass 438.166511; found 438.164993. Anal. Calcd for $C_{23}H_{23}N_3O_6\cdot 0.55CH_3OH$: C, 62.16; H, 5.58; N, 9.23. Found: C, 62.39; H, 5.20; N, 8.86.

Procedure for Preparation of Resin 10. A 25-mL single-necked round-bottomed flask equipped with a magnetic stirring bar, a septum, an argon inlet, and an argon outlet was charged with (*S*)-(−)-4-benzyl-2-oxazolidinone (12 equiv). The flask was purged with argon, charged with anhyd THF, and cooled to −78 °C. A 1.6 M solution of *n*-BuLi in hexanes (10 equiv) was added dropwise with stirring. The mixture was stirred for 15 min at −78 °C, **9** (X = O, R = allyl) was added to the reaction mixture, and the suspension was stirred for 2 h at −78 °C. The reaction flask was then charged with benzyl bromide (15 equiv), and the reaction mixture was stirred at −78 °C for 5 min. The dry ice/acetone bath was removed, allowing the reaction mixture to warm to rt. The reaction flask was then placed in a preheated sand bath (65 °C), and the reaction was shaken for 2 days, keeping the temperature constant. The reaction flask was removed from the sand bath allowing the mixture to cool to rt. The reaction mixture was quenched upon addition of an aqueous 5% NH_4Cl solution and filtered into a polypropylene-fritted tube, and the resin was collected and washed thoroughly (1.5−2.0 mL volumes) with IPA (3×), DCM (3×), IPA (3×), DCM (3×), IPA (3×), and $CHCl_3$ (3×), and dried.

(3*S*)-1-*N*-Benzyl-4-*N*-(allyloxycarbonyl)-3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**10**) (45% yield from **5b**, theoretical loading of 0.577 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 12.93 (brs, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.51 (s, 1H), 7.31−7.12 (m, 5H), 6.00−5.88 (m, 1H), 5.31−5.29 (m, 1H), 5.25−5.17 (m, 3H), 5.10−5.03 (m, 1H), 4.96 (d, J = 16 Hz, 1H), 4.66 (d, J = 5.1 Hz, 2H), 1.18 (d, J = 7.0 Hz, 3H); ^{13}C NMR [$(CD_3)_2SO$]: δ 167.5, 166.3, 152.0, 136.2, 132.4, 131.3, 129.1, 128.8, 127.5, 127.2, 126.0, 124.4, 124.2, 118.1, 116.7, 66.8, 52.8, 44.8, 15.5; mass spectrum (ESIMS), *m*/*z* 381 [(M + H)$^+$]. HRMS [(M + H)$^+$]: Calcd mass 381.145047; found 381.143634. Anal. Calcd for $C_{21}H_{20}N_2O_5\cdot 0.3C_2HF_3O_2$: C, 62.58; H, 4.94; N, 6.76. Found: C, 62.55; H, 4.97; N, 6.70. Chiral HPLC analysis of **10** was performed at 254 nm using a Chiralcel OJ column and 80% hexanes, 20% IPA, and 0.1% TFA as eluent at a flow rate of 1.0 mL/min at rt.

Procedure for Preparation of Resin 11. A single-necked round-bottomed flask was charged with Wang resin (**1**), an Fmoc protected amino acid (2 equiv), DIEA (2 equiv), HBTU (2 equiv) and anhyd DMF (1 mL/100 mg of resin). The flask was shaken overnight at rt, and the resin was then filtered, washed thoroughly with DMF (2×), DCM (2×), IPA (2×), DMF (2×), DCM (2×), and IPA (2×), and dried. The resin was transferred to a 50-mL single-necked round-bottomed flask and suspended in a 20% piperidine/DMF solution for 10 min at rt. The resin was then filtered, washed thoroughly with DMF (2×), DCM (2×), IPA (2×), DMF (2×), DCM (2×), and IPA (2×), and dried by passing air through it.

Procedure for Preparation of Resin 12. A single-necked round-bottomed flask was charged with **11**, FNBA (2 equiv), DCC (2.5 equiv), and DCM (1 mL/100 mg of resin) in the presence of a catalytic amount of DMAP. The flask was shaken overnight at rt, and the resin was then filtered, washed thoroughly with hot DMF (2×), IPA (2×), hot DMF (2×), DCM (2×), and IPA (2×), and dried.

2-[(4-Fluoro-3-nitrophenyl)carboxamido]acetic acid (**12a**) (61% yield from **1,** theoretical loading of 0.627 mmol/g): ^{1}H NMR [$(CD_3)_2SO$]: δ 12.68 (brs, 1H), 9.23 (t, J = 5.7 Hz, 1H), 8.62 (dd, J = 7.3, 2.2 Hz, 1H), 8.28−8.23 (m, 1H), 7.70 (dd, J = 11 Hz, 1H), 3.93 (d, J = 5.5 Hz, 2H); ^{13}C NMR [$(CD_3)_2SO$]: δ 171.3, 164.0, 158.5, 155.0, 137.2, 137.1, 135.7, 135.5, 131.0, 125.8, 119.5, 119.2, 41.8; mass spectrum (ESIMS), *m*/*z* 241 [(M − H)$^-$]. HRMS [(M + H)$^+$]: Calcd mass 243.041725; found 243.040897.

Supporting Information Available: Spectroscopic data for **12a** and **15c** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead for ordering information.

JO971688+