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Diastereodivergent synthesis of chiral tetrahydropyrrolodiazepinediones *via* a one-pot intramolecular aza-Michael/lactamization sequence

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Abstract

A modular and diastereodivergent synthesis of tetrahydro-1*H*-pyrrolo[1,2*d*]diazepin(2,5)-diones is presented. The tetrahydropyrrolodiazepindione scaffold is obtained *via* a base-mediated three-step isomerization/tandem cyclization of amino acid-coupled homoallylic amino esters.

Diastereoselectivity of the process is mediated by the interplay of a kinetic cyclization event and a propensity for thermodynamic epimerization at two labile chiral centers, giving rise to two distinct major diastereomers dependent on starting material stereochemistry and reaction conditions selected. Herein, we present a synthetic and computational study for this tandem process on a variety of amino ester substrates.

Graphical Abstract

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The authors declare no competing financial interests.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Mechanistic analysis, computational methods and data, X-ray refinement data, 2D structural assignments for select compounds, and copies of ¹H and ¹³C NMR spectra for all products (PDF)

X-ray structure (cif)

INTRODUCTION

Diversity-oriented synthesis relies on the rapid and efficient assembly of unique three-dimensional molecular scaffolds from modular, stereochemically well-defined building blocks.¹ Such building blocks may be obtained from asymmetric synthetic methodologies as well as nature's "chiral pool." We have previously reported studies employing chiral homoallylic amino- and hydroxy-esters, obtained *via* asymmetric crotylation of aldehydes and imines, as reliable synthons for the assembly of diverse polyketide-like molecular libraries.^{2–3} In the course of a reaction screening campaign targeting challenging intramolecular lactamization of amino-acid-coupled homoallylic amine **1** to form **2**, we have discovered a highly diastereoselective and diastereodivergent one-pot, three-step intramolecular cyclization sequence that gives rise to tetrahydro-1*H*-pyrrolo[1,2-*d*][1,4]diazepine-(2,5)-diones of type **3** (Scheme 1). In the literature, examples of synthetic tetrahydropyrrolo[1,2-*d*][1,4]diazepinones are limited in scope, with isolated reports from Paquette and Scott in 1968,⁴ Lavagnino and Ryan in 1983,⁵ and Gurn in 1985.⁶ Fobian and Moeller have also reported the synthesis of chiral bicyclic piperazinones *via* intramolecular, reductive amination of aldehyde-tethered substrates derived from proline-derived dipeptides.⁷ More recently, Sheng and coworkers described the unexpected production of tetrahydropyrrolodiazepinones through acid-induced rearrangement of pyrrolo-oxazocines.⁸ Lubell and coworkers have developed a three-step synthesis of pyrrolodiazepinones from α -aminoacyl- β -amino esters,⁹ and in 2015 demonstrated the utility of these compounds, which possess dihedral ϕ/ψ angles reminiscent of an ideal inverse γ -turn,^{10–11} as peptidomimetic modulators of vasoconstriction.¹² Given that the peptidomimetic tetrahydropyrrolodiazepinone scaffold is an underutilized heterocycle in the context of diversity-oriented library synthesis, we have sought to further explore efficient and stereochemically well-defined tandem reactions to access these compounds.

RESULTS AND DISCUSSION

Initial reaction screening efforts to obtain macrolactam **2** focused on conditions known to effect transamidations or transesterifications¹³ including zirconium (IV) catalysis with hydroxypyridine,^{14–15} tin-mediated transesterifications,¹⁶ and treatment with anionic acyl transfer catalysts¹⁷ produced *in situ* by reaction of various heterocycles with DBU. While none of the screened conditions produced the desired 10-membered macrocycle **2**, we identified a subset of DBU/triazole acyl transfer reaction conditions that produced a new product. NMR analysis suggested the bicyclic structure (*S,S*)-**3a**, which was later confirmed by X-ray crystallography (Figure 1A). Notably, and similar to Lubell's pyrrolodiazepinones, tetrahydropyrrolodiazepindione (*S,S*)-**3a** contains peptidic dihedral angles ($\phi = -74^\circ$ and $\psi = 73^\circ$) within range of an ideal inverse γ -turn ($\phi -70^\circ$ to -85° , $\psi 60^\circ$ to 70° , Figure 1B).^{10–11}

Preliminary optimization studies utilizing UPLC/MS for analysis indicated the greatest conversion of **1a** (initially used as the HCl salt) to **3a** occurred on treatment with two equivalents of DBU in CH₃CN with microwave heating (145 °C, 45 minutes). Using these conditions, product **3a** was isolated in 2.7:1 crude d.r., and was then chromatographically

purified to a single diastereomer in 63% yield (Scheme 2). The minor diastereomer observed in the crude, later identified to be (*R,R*)-**3a** (*vide infra*), was not isolated.

In order to evaluate the scope of this transformation, a small series of substrates was synthesized with variation of both homoallylic amine and amino acid building blocks (Scheme 3). Alloc-protected homoallylic amines **7-9** were first prepared from enantioenriched crotylsilane **4**¹⁸ *via* asymmetric crotylation of a variety of Alloc imines, generated *in situ* from aldehydes **5a-c** and allyl carbamate (**6**).

After Pd(0)-mediated Alloc deprotection, the amines were coupled (HATU/DIPEA) to various Boc-protected *D*- and *L*-amino acids to afford Boc-protected substrate precursors **10a-g** (Scheme 4 and Table 1). Removal of the Boc group with silica-supported TsOH (SCX) resin gave the deprotected amino esters **1a-g**, which were immediately carried on to cyclization studies as the free base without further purification (Scheme 4).

Initial substrate scope studies were performed on *L*-amino acid-derived (*S*)-**10b**, (*S*)-**10c**, and (*S*)-**10d**. Disappointingly, under microwave-mediated conditions, these substrates all produced intractable mixtures of what appeared to be three or more diastereomers of the pyrrolodiazepinone **3**. We attributed these mixtures to both a lack of diastereoselectivity in the pyrrolidine ring formation, as well as possible epimerization of the acidic amino acid α -center. We next attempted to identify milder conditions to improve diastereoselectivity using (*S*)-**10b** as a model substrate. In order to better understand the sequence of the three-step transformation, we first performed *in situ* NMR analysis following treatment of (*S*)-**1b** with DBU (CD₃CN, room temperature) and observed that the unsaturated amide rapidly isomerizes to the conjugated isomer (*S*)-**11b** (Scheme 5). Accordingly, we initially envisioned the reaction occurring through one of two three-step sequences: Pathway A entails double bond isomerization to (*S*)-**11b**, followed by intramolecular lactamization and subsequent transannular cyclization¹³ of macrocycle (*S*)-**12b**; conversely in Pathway B, after isomerization to (*S*)-**11b**, an intramolecular *aza*-Michael reaction would give pyrrolidine (*S,S*)-**13b** with subsequent 7-membered lactam formation to afford (*S,S*)-**3b**. On heating substrate (*S*)-**1b** to 100 °C in CD₃CN with one equivalent of DBU, full disappearance of all olefinic protons was observed in ¹H NMR, prior to complete lactamization (loss of methanol) as determined by LC/MS analysis of an aliquot taken at the same time point. We thus excluded macrocycle (*S*)-**12b** as a major intermediate, and presumed the three-step sequence to predominantly occur *via* pyrrolidine (*S,S*)-**13b** (Pathway B).

Pathway B thus renders the intramolecular *aza*-Michael reaction a key diastereodetermining event. Young and coworkers have shown that the diastereomeric control of intramolecular *aza*-Michael reactions to form six membered rings can be divergent, depending on the impact of reagents used and the sterics of the six-centered transition state.¹⁹⁻²⁰ Analysis of the conformations preceding a five-centered transition state formation (Scheme 6) that would give rise to the two possible pyrrolidine diastereomers **13b** suggests that the conformation producing the observed stereochemistry ((*S,2S*)-**13b**) lacks a disfavorable 1,3-diaxial interaction between the methyl substituent and the vinylic C-H of the Michael acceptor, which is present in the conformation giving rise to the analogous product ((*S,2R*)-**13b**).

Despite this possible kinetic rationale for diastereoselectivity, the observation of more than two diastereomers under forcing conditions implied epimerization at the acidic amino acid α -center along with a possible *via* retro-*aza*-Michael processes to thermodynamically equilibrate the pyrrolidine chiral center; similar processes have been demonstrated in the literature.^{21–24} For simplification, we first focused on potential thermodynamic equilibration of the pyrrolidine, using DFT analysis²⁵ (B3LYP-6–31g**) in order to compare the relative Gibbs free energies of the possible product and intermediate diastereomers for the intermediate pyrrolidines **13** (Table 2).

Our DFT calculations indicate that there is no consistent trend for thermodynamic control of the intermediate pyrrolidine stereochemistry; the (*2R*) or (*2S*) diastereomer is thermodynamically favorable to varying degrees, depending on amino acid sidechain composition and stereochemistry. We postulated, then, that conditions disfavorable to the thermodynamic equilibration of **13** should give rise to improved diastereoselectivity, in the formation of the kinetically favored (*2S*) product for other substrates. Our efforts to optimize the reaction parameters for substrate (*S*)-**1b** according to this assumption are summarized in Table 3. In agreement with our kinetic hypothesis, lowering the reaction temperature to 60 °C did improve diastereoselectivity, albeit with slower conversion (48 h reaction times). Rate enhancement through increased equivalents of DBU also gave a remarkable improvement in diastereoselectivity at 25 °C, but there was still limited conversion to product after 18 h. Gratifyingly, heating the same conditions to 100 °C gave the desired product in 91% yield after 90 minutes, with a negligible drop in diastereoselectivity in comparison to the room temperature conditions.

We next explored the scope and diastereoselectivity of these improved conditions on a range of other substrates; the results are summarized in Figure 2. The transformation proceeded smoothly for substrates substituted with both aliphatic and aromatic *L*-amino acid sidechains. Notably, *L*-valine derived substrate (*S*)-**1c** produced bicyclic compound (*S,S*)-**3c** with no other diastereomers detected; this outcome can potentially be rationalized by the DFT calculations, as the two *L*-valine pyrrolidines were the only observed case wherein the (*2S*) (kinetic) pyrrolidine is also significantly thermodynamically favored relative to the (*2R*) pyrrolidine (by approximately 1.3 kcal/mol). We propose that this kinetic/thermodynamic match leads to the exclusive formation of only one diastereomer. We also examined one *D*-amino acid-derived substrate, *D*-leucine substituted (*R*)-**1b**. Disappointingly, under the optimized conditions this substrate produced an inseparable mixture of two diastereomers with a significantly poorer d.r of 3:1, which curiously appeared to favor the same (*S,S*)-**3b** product that was obtained from (*S*)-**1b**.

In an effort to identify conditions that would impart improved diastereoselectivity for the *D*-amino acid derived substrates, we next examined NaOMe, a strong base capable of effecting double bond isomerizations, *aza*-Michael reactions, and transamidations.²⁶ Treatment of substrate (*R*)-**1b** with NaOMe in both THF and DMF at –78 °C rapidly afforded the desired pyrrolodiazepinone in excellent yields. As compared to the DBU conditions, treating (*R*)-**1b** with sodium methoxide and THF as solvent shifted the product ratio to a 1.4:1 mixture of (*S,S*)-**3b** and (*R,R*)-**3b** (Table 4, Entry 2). Interestingly, the ratio shifted to favor the (*R,R*)-**3b** diastereomer with the use of sodium methoxide and DMF as solvent (Table 4,

Entry 3). In contrast to the diastereodivergence observed with the (*R*)-substrates, the *L*-amino acid-derived substrates (*S*)-**1a** and (*S*)-**1b** produced the same major diastereomers (*S,S*)-**3a** and (*S,S*)-**3b** under the NaOMe conditions as had been observed previously under the DBU conditions, albeit with differing degrees of diastereoselectivity (Table 4, Entries 4 and 5, and Figures 2 and 3).

Using the optimized NaOMe/DMF conditions, similar reactivity favoring the (*R,R*) diastereomer was observed with other *D*-amino acid substrates (*R*)-**1a**, and (*R*)-**1c-f** as summarized in Figure 3. In summary, these results suggested that following an initial aza-Mannich reaction and subsequent macrolactamization, epimerization of the amino acid α -center occurs to afford only two of four possible diastereomeric bicyclic cores as major products in varying ratios, dependent upon both stereochemistry of substrate and the conditions used.

In order to determine a possible cause for the observed diastereodivergent pathways, we performed additional DFT calculations examining the relative thermodynamic stabilities of the product diastereomers **3**. These relative energy values are presented in Table 5; in all cases, the (*R,R*) diastereomer is the thermodynamically most stable, followed by the (*S,S*) diastereomer which is only slightly (0.5 kcal/mol) higher in energy. The remaining two diastereomers, which were not cleanly isolated under any conditions examined for these substrates, are considerably higher in energy.

Based on these trends, our proposed mechanistic scheme depicting the envisioned global equilibria is presented in Scheme 7. From diastereomers (*S*)-**1b**/(*R*)-**1b**, following the initial pyrrolidine formation step (presumed to kinetically favor the *cis* product in all cases), the possibility of thermodynamic equilibration at each intermediate allows for the funneling into one of two thermodynamic wells: the observed products (*S,S*)-**3b** and (*R,R*)-**3b**. The degree of thermodynamic equilibration that occurs at each step, presumably mediated by several factors including sterics, base strength, ring strain and solvent effects, ultimately determines the final diastereomeric distribution. For substrate (*S*)-**1b**, the kinetically favored pyrrole cyclizes to give thermodynamically favored product (*S,S*)-**3b**, representing a “matched” scenario. The compound (*R,R*)-**3b**, obtained *via* lactamization of the thermodynamically favored pyrrole (*R,2R*)-**11b**, has two potential downhill routes for equilibration: (1) a retro-*aza*-Michael/*aza*-Michael pathway to give rise to the observed major diastereomer (*S,S*)-**3b**, or (2) α -epimerization of the amino acid center to give compound (*R,R*)-**3b**, the observed minor diastereomer. Conversely, *D*-leucine-coupled substrate (*R*)-**2b** undergoes a kinetically favored cyclization to give intermediate (*R,2S*)-**11b**, which has a larger thermodynamic driving force (0.6 kcal/mol) for retro-*aza*-Michael epimerization of the pyrrolidine intermediate than its (*S*)-diastereomer, as well as two energetically downhill epimerization pathways away from (*R,S*)-**3b**, one producing (*S,S*)-**3b**, the other producing (*R,R*)-**3b**. In contrast, conditions favoring the thermodynamic equilibration to pyrrolidine (*R,2R*)-**11b** would then, upon lactamization, produce bicyclic product (*R,R*)-**3b**, a thermodynamic well. Reaction conditions optimized to favor the “kinetic” pyrrolidine formation for the (*S*)-isomer lead to a kinetic/thermodynamic mismatch for the (*R*)-isomer, with product ratios dependent upon the proportion of substrates progressing along the two thermodynamically downhill epimerizations. While it is difficult to attribute the improved (*R*)-isomer diastereomeric

ratios under the NaOMe/DMF conditions, it may be that the increased basicity enables the intermediate pyrrole (*R*)-**11b** to equilibrate more rapidly to the highly thermodynamically-favored (*R*,*2R*)-**11b** product, improving diastereoselectivity toward the final product (*R*,*R*)-**3b**. Similar base-dependent processes leading to diastereodivergent reaction outcomes have been reported by Bradshaw and coworkers in the diastereodivergent construction of 5-oxodecahydroquinolines *via* intramolecular *aza*-Michael reactions,²⁷ as well as Galvez and coworkers in the Wadsworth-Emmons construction of alkylidene piperidines.²⁸

As a final study, we examined the reactivity of proline-substituted substrates **1g** under our optimized sets of conditions (Table 6). Following Boc deprotection and cyclization, *L*-proline-derived substrate (*S*)-**10g** afforded the expected compound (*S*,*S*)-**3g** as the major product under both sets of conditions. In addition, *D*-proline-derived substrate (*R*)-**10g** reacted as expected under the sodium methoxide conditions, affording compound (*R*,*R*)-**3g** in 50% yield with 4:1 diastereoselectivity. However, in contrast to all of the substrates derived from acyclic *D*-amino acids, (*R*)-**10g** produced a third distinct diastereomer as a major product when subjected to the DBU/CH₃CN conditions. This diastereomer was assigned as (*5aR*,*11aS*)-**3g** based on 2D NMR analysis and DFT-predicted NMR spectra.¹

Revisiting the global equilibria as depicted in Scheme 7, we hypothesize that for proline-derived substrates, the constrained pyrrolidine ring creates sufficient steric congestion to prevent the α epimerization of the amino acid center by the more hindered, weaker base DBU, thus preventing the conversion of (*5aR*,*11aS*)-**3g** to (*5aS*,*11aS*)-**3g** as is postulated to occur under DBU-mediated conditions with other *D*-amino acid sidechains (Scheme 8). Consistent with this hypothesis, we found that treatment of isolated (*5aR*,*11aS*)-**3g** with NaOMe in DMF (a less hindered, stronger base) quantitatively produces (*5aS*,*11aS*)-**3g** as a major product. In this experiment, there was no discernable change in the quantified amount of (*5aR*,*11aR*)-**3g** in the resultant diastereomeric mixture, suggesting that for this substrate, the α -epimerization is kinetically favored relative to the retro-*aza*-Michael epimerization to (*5aR*,*11aR*)-**3g**, which is slightly more thermodynamically downhill (0.6 kcal/mol *vs.* 1.0 kcal/mol).

CONCLUSION

In summary, we have developed a highly modular and diastereodivergent route to chiral pyrrolidiazepinones. Diastereoselectivity in this efficient three-step transformation can be tuned by the selection of starting material stereochemistry and reaction conditions to afford to distinct diastereomers of this underexplored bicyclic, peptidomimetic heterocycle. Efforts to further utilize this unique tandem transformation in the context of diversity oriented library synthesis and peptidomimetic applications including pyrrolidiazepinone libraries are currently underway and will be reported in due course.

EXPERIMENTAL SECTION

1. General information.

All ¹H NMR and ¹³C NMR spectra were recorded using Varian Unity Plus 400 or Varian Unity Plus 500 spectrometers at ambient temperature. Chemical shifts are reported in parts

per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant and integration. Infrared spectra were recorded on Nicolet Nexus 670 FT-IR ESP spectrophotometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm and reported as $[\alpha]^{23}_D$ (concentration in g/100 mL solvent). High resolution mass spectrometry data was obtained on a Waters Qtof (hybrid quadrupolar/time-of-flight) API US system by electrospray (ESI) in the positive mode. Mass correction was done by an external reference using a Waters Lockspray accessory. Analytical thin layer chromatography was performed using EMD 0.25 mm silica gel 60-F plates. Flash column chromatography was performed on Sorbent Technologies 60 Å silica gel. All reactions were performed under an atmosphere of nitrogen or argon with magnetic stirring. Dichloromethane and tetrahydrofuran were obtained from a dry solvent system (alumina). Anhydrous acetonitrile and dimethylformamide were obtained from Sigma-Aldrich and used without further purification. SiliaBond® Tosic Acid (SCX) resin was obtained from Silicycle, Inc. Macroporous Tosic Acid (MP-TsOH) resin was obtained from Waters, Inc. All microwave experiments were performed on a CEM Discover microwave reactor, using a sealed 10- or 35-mL vessel with temperatures monitored by an external sensor.

General Procedure A: To a flame-dried, nitrogen-purged flask equipped with a stir bar was added allyl carbamate (1.0 equiv). Anhydrous CH_2Cl_2 was added, followed by the requisite aldehyde **5a**, **5b**, or **5c**. The reaction mixture was cooled to -78°C and BF_3 -diethyl etherate was slowly added *via* syringe. The reaction was stirred at -78°C for 30 minutes. Crotylsilane **4** was added and the reaction vessel was transferred to a chiller set to -35°C . The reaction was stirred at this temperature for 48–72 h, tracking by TLC analysis. Upon completion, the reaction mixture was carefully quenched with the addition of saturated aqueous sodium bicarbonate and extracted three times with CH_2Cl_2 . The combined organic fractions were washed with brine, dried over sodium sulfate, and condensed to give a crude product that was then purified by ISCO flash column chromatography using a prepacked 80 g silica cartridge. Products were eluted using a gradient of 15%–27% ethyl acetate in hexanes over 15 minutes, followed by 40% ethyl acetate in hexanes for 5 minutes.

Methyl (5S,6R,E)-6-(((allyloxy)carbonyl)amino)-5-methyl-6-phenylhex-3-enoate (7): Obtained as a clear oil (1.16 g, 90% yield, 10:1 d.r.) from benzaldehyde **5a** utilizing General Procedure A. $[\alpha]^{23}_D +38$ (c 0.39, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.24–7.16 (m, 2H), 7.16–7.10 (m, 3H), 5.81 (s, 2H), 5.46 (td, $J = 6.6, 15.4$ Hz, 1H), 5.27 (dd, $J = 8.0, 15.4$ Hz, 1H), 5.19 (d, $J = 16.8$ Hz, 1H), 5.08 (d, $J = 10.6$ Hz, 1H), 4.58 (t, $J = 7.4$ Hz, 1H), 4.48 (dd, $J = 5.9, 13.3$ Hz, 1H), 4.41 (dd, $J = 4.3, 13.3$ Hz, 1H), 3.57 (s, 3H), 2.91 (d, $J = 6.6$ Hz, 2H), 2.56 (tdd, $J = 7.0, 7.4, 8.0$ Hz, 1H), 0.92 (d, $J = 7.0$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 171.7, 155.2, 140.0, 135.2, 127.7, 126.9, 126.7, 123.0, 117.0, 65.0, 58.9, 51.4, 41.6, 37.3, 16.2. HRMS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{18}\text{H}_{23}\text{NO}_4\text{Na}$, 340.1525; found, 340.1528. IR (thin film): 3338, 1770, 1700 cm^{-1} .

Methyl (5S,6R,E)-6-(((allyloxy)carbonyl)amino)-6-(3-bromophenyl)-5-methylhex-3-enoate (8): Obtained as a clear oil (2.21 g, 73% yield, >20:1 d.r.) from 3-bromobenzaldehyde **5b** utilizing General Procedure A. $[\alpha]^{23}_D +71$ (c 4.5, CHCl_3); ^1H NMR

(400 MHz, CDCl₃) δ 7.37 (d, J = 7.6 Hz, 1H), 7.32 (s, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 5.85 (tdd, J = 5.6, 10.2, 16.7 Hz, 1H), 5.52 (td, J = 6.6, 15.6 Hz, 1H), 5.27 (dd, J = 8.0, 15.6 Hz, 1H), 5.24 (d, J = 16.7 Hz, 1H), 5.14 (br d, J = 10.2 Hz, 1H), 4.57 (dd, J = 7.0, 8.6 Hz, 1H), 4.51 (br dd, J = 5.5, 13.5 Hz, 1H), 4.46 (dd, J = 5.5, 13.5 Hz, 1H), 3.63 (s, 3H), 2.97 (d, J = 6.6 Hz, 2H), 2.55 (qd, J = 7.0, 8.0 Hz, 1H), 0.93 (d, J = 7.0 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 171.9, 155.3, 142.6, 135.7, 134.8, 132.6, 130.0, 129.5, 125.8, 123.8, 122.1, 117.5, 65.5, 58.5, 51.7, 41.6, 37.4, 16.3. HRMS (m/z): [M+Na]⁺ calcd. for C₁₈H₂₂BrNO₄Na, 418.0630; found, 418.0623. IR (thin film): 3328, 1700, 1527 cm⁻¹.

Methyl (5S,6S,E)-6-(((allyloxy)carbonyl)amino)-6-cyclopropyl-5-methylhex-3-enoate (9): Obtained as a clear oil (2.11 g, 98% yield, 12:1 d.r.) from cyclopropanecarbaldehyde **5c** utilizing General Procedure A. [α]_D²³ -24 (c 9.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.78 (tdd, J = 5.5, 10.5, 17.0 Hz, 1H), 5.48–5.42 (m, 2H), 5.15 (dd, J = 1.2, 17.0 Hz, 1H), 5.09–5.02 (m, 2H), 4.40 (br d, J = 5.5 Hz, 2H), 3.54 (s, 3H), 2.93 (d, J = 5.0 Hz, 2H), 2.91–2.82 (m, 1H), 2.34 (sxt, J = 6.2 Hz, 1H), 0.96 (d, J = 7.0 Hz, 3H), 0.66 (dtd, J = 4.3, 8.2, 12.9 Hz, 1H), 0.46–0.34 (m, 1H), 0.30–0.19 (m, 1H), 0.19–0.10 (m, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 171.9, 155.6, 135.9, 132.8, 122.3, 116.8, 64.9, 58.9, 51.4, 41.8, 37.4, 16.4, 12.8, 4.5, 1.3. HRMS (m/z): [M+Na]⁺ calcd. for C₁₅H₂₃NO₄Na, 304.1525; found, 304.1524. IR (thin film): 3334, 1697, 1524 cm⁻¹.

General Procedure B: Alloc Deprotection. Alloc-protected substrate **7**, **8**, or **9** was dissolved in a 3:1 CH₂Cl₂:CH₃OH solution (final concentration 0.4 M). 1,3-dimethylbarbituric acid (1.1 equiv) was added and the reaction was stirred for 5 minutes. Tetrakis(triphenylphosphine)palladium(0) (5 mol %) was added in one portion and the reaction was stirred at room temperature until TLC analysis indicated full consumption of starting material (approximately 2 h). MP-TsOH resin (3 mmol/g resin loading, 4 equiv, 1.2 grams resin per millimole substrate) was added in one portion and the reaction was stirred at room temperature for one hour. The resin was isolated by filtration, rinsing three times with CH₂Cl₂. After returning the resin to the flask, a solution of 10% Et₃N in CH₃OH (10 mL per gram of resin) was added. The suspension was stirred for one hour, filtered and the one hour resin treatment was repeated with a fresh portion of 10% Et₃N in methanol followed by another filtration. Both mother liquors were combined and condensed to give the intermediate deprotected amines **S1-S3** as orange oils. Compounds **S1-S3** were not shelf-stable and were carried on to the amino acid coupling step immediately without further purification.

General Procedure C: HATU-mediated coupling. Compounds **S1-S3** were dissolved in CH₂Cl₂ (0.2M concentration) at room temperature under an atmosphere of nitrogen. The requisite Boc-protected amino acid (1.1 equiv) was added, followed by HATU (1.2 equiv) and *N,N*-diisopropylethylamine (2.5 equiv). After stirring at room temperature overnight, the reaction was condensed onto silica gel and purified by ISCO flash chromatography using a gradient of 30% to 50% ethyl acetate in hexanes (over the default runtime for the size column used) to give amino acid-protected substrates **10a-g**.

Methyl (5S,6R,E)-6-((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-5-methyl-6-phenylhex-3-enoate ((S)-10a).: Obtained as a pale yellow solid (300 mg, 49% yield, two steps) after deprotection of compound **7** to afford compound **S1** (General Procedure B), which was immediately coupled with Boc-*L*-phenylalanine (General Procedure C). mp = 105–107 °C; $[\alpha]_D^{23} +117$ (*c* 3.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 5.4:1 mixture of Boc rotamers. Major Rotamer: δ 7.29–7.16 (m, 8H), 7.10–7.05 (m, 2H), 6.77 (br d, *J* = 7.8 Hz, 1H), 5.28–5.19 (m, 2H), 5.15 (br d, *J* = 8.6 Hz, 1H), 4.80 (br dd, *J* = 5.1, 7.4 Hz, 1H), 4.40 (br td, *J* = 6.6, 8.6 Hz, 1H), 3.68 (s, 3H), 3.10–2.96 (m, 3H), 2.94 (d, *J* = 7.0 Hz, 2H), 1.38 (s, 9H), 0.84 (m, 3H); Minor Rotamer: δ 7.77 (d, *J* = 7.8, 1H), 7.70 (d, *J* = 7.8, 1H), 7.45–7.34 (m, 3H), 7.29–7.16 (m, 1H), 7.15–7.13 (m, 2H), 7.13–7.11 (m, 1H), 5.48–5.38 (m, 2H), 5.12–5.05 (m, 2H), 4.78–4.73 (m, 1H), 4.60 (brq, *J* = 5.9 Hz, 1H), 3.68 (s, 3H), 3.21 (dd, *J* = 5.9, 14.5 Hz, 1H), 3.10–2.96 (m, 1H), 2.92–2.89 (m, 1H), 2.86 (ddd, *J* = 1.6, 7.8, 16.0 Hz, 1H), 2.71 (ddd, *J* = 1.4, 7.1, 16.0 Hz, 1H), 1.37 (s, 9H), 0.84 (m, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃, mixture of rotamers, all peaks reported) δ 174.0, 172.4, 170.8, 170.3, 155.4, 155.2, 139.2, 139.0, 136.8, 136.2, 135.4, 134.4, 129.4, 128.5, 128.4, 128.0, 127.5, 127.5, 127.1, 126.8, 126.5, 126.0, 123.7, 121.8, 117.3, 111.0, 80.0, 79.8, 57.6, 56.9, 56.0, 54.2, 52.1, 51.9, 41.6, 38.4, 37.9, 37.3, 36.5, 32.7, 29.6, 28.2, 17.5, 16.5; HRMS (*m/z*): [M+Na]⁺ calcd. for C₂₈H₃₆N₂O₅Na, 503.2522; found, 503.2534. IR (thin film): 3315, 1738, 1698, 1655, 745, 700 cm⁻¹.

Methyl (5S,6R,E)-6-((R)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-5-methyl-6-phenylhex-3-enoate ((R)-10a).: Obtained as a pale yellow solid (335 mg, 54% yield, two steps) after deprotection of compound **7** to afford compound **S1** (General Procedure B), which was immediately coupled with Boc-*D*-phenylalanine (General Procedure C). mp 110–112 °C; $[\alpha]_D^{23} +3.6$ (*c* 4.7, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 5:1 mixture of Boc rotamers. Major Rotamer: δ 7.30–7.08 (m, 8H), 7.06–6.95 (m, 2H), 6.85 (br d, *J* = 8.2 Hz, 1H), 5.55–5.47 (m, 1H), 5.41 (td, *J* = 7.0, 15.6 Hz, 1H), 5.26 (d, *J* = 8.2, 15.6 Hz, 1H), 4.90 (dd, *J* = 6.6, 8.6 Hz, 1H), 4.48–4.36 (m, 1H), 3.96 (s, 3H), 3.11–2.91 (m, 4H), 2.57 (sxt, *J* = 6.9 Hz, 1H), 1.46–1.35 (m, 9H), 0.9 (d, *J* = 6.9 Hz, 1H); Minor Rotamer: δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.46–7.37 (m, 2H), 7.30–7.08 (m, 6H), 5.55–5.45 (m, 1H), 5.21–5.16 (m, 1H), 5.11 (d, *J* = 8.2 Hz, 1H), 4.62 (q, *J* = 7.0 Hz, 1H), 3.72 (s, 3H), 3.22 (dd, *J* = 5.0, 13.7 Hz, 1H), 3.11–2.91 (m, 3H), 2.85–2.78 (m, 1H), 1.46–1.35 (m, 9H), 0.93 (d, *J* = 6.6 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃, mixture of rotamers, all peaks reported) δ 174.3, 172.9, 172.7, 171.0, 170.7, 155.6, 155.3, 140.5, 139.0, 138.8, 136.7, 136.2, 135.4, 134.7, 129.4, 128.5, 128.1, 127.4, 127.2, 126.9, 126.7, 123.8, 122.0, 117.3, 111.2, 80.0, 79.9, 57.5, 57.0, 56.9, 56.0, 54.3, 52.0, 51.9, 41.6, 38.2, 38.0, 37.4, 36.7, 32.9, 28.3, 17.8, 16.3 HRMS (*m/z*): [M+Na]⁺ calcd. for C₂₈H₃₆N₂O₅Na, 503.2522; found, 503.2518. IR (thin film): 3308, 1714, 1521, 734, 700, 667 cm⁻¹.

Methyl (5S,6R,E)-6-((S)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-5-methyl-6-phenylhex-3-enoate ((S)-10b).: Obtained as an amorphous yellow solid (275 mg, 52% yield, two steps) after deprotection of compound **7** to afford compound **S1** (General Procedure B), which was immediately coupled with Boc-*L*-leucine (General Procedure C). $[\alpha]_D^{23} -3.6$ (*c* 2.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 7:1 mixture of Boc rotamers. Major Rotamer: δ 7.31–7.24 (m, 2H), 7.23–7.18 (m, 1H), 7.17–7.13 (m, 2H), 7.07 (br d, *J* =

7.4 Hz, 1H), 5.51 (td, $J = 7.0, 15.6$ Hz, 1H), 5.31 (dd, $J = 8.0, 15.6$ Hz, 1H), 4.91 (dd, $J = 6.3, 9.0$ Hz, 1H), 4.21–4.08 (m, 1H), 3.66 (s, 3H), 3.01–2.97 (m, 2H), 2.60 (sxt, $J = 6.8$ Hz, 1H), 1.80–1.50 (m, 3H), 1.42 (s, 9H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.89–0.84 (m, 6H); Minor Rotamer δ 7.44 (br d, $J = 8.6$ Hz, 1H), 7.31–7.24 (m, 2H), 7.23–7.18 (m, 1H), 7.17–7.13 (m, 2H), 5.53–5.45 (m, 1H), 5.29–5.20 (m, 1H), 5.03 (br d, $J = 8.6$ Hz, 1H), 4.87 (dd, $J = 5.9, 8.6$ Hz, 1H), 4.32 (dt, $J = 5.1, 8.6$ Hz, 1H), 3.68 (s, 3H), 3.05–3.01 (m, 1H), 2.99–2.93 (m, 1H), 2.88–2.80 (m, 1H), 1.80–1.50 (m, 3H), 1.42 (s, 9H), 0.97–0.84 (m, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3 , mixture of rotamers, all peaks reported) δ 175.9, 172.6, 171.9, 155.9, 155.7, 139.6, 135.6, 134.8, 128.0, 127.3, 127.0, 123.5, 121.8, 79.8, 57.2, 56.7, 53.1, 51.8, 41.7, 40.6, 37.4, 36.8, 32.8, 29.6, 28.2, 24.6, 22.8, 21.9, 17.8, 16.1; HRMS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{25}\text{H}_{38}\text{N}_2\text{O}_5\text{Na}$, 469.2678; found, 469.2682. IR (thin film): 3270, 1742, 1691, 1642, 701 cm^{-1} .

Methyl (5S,6R,E)-6-((R)-2-((tert-butoxycarbonyl)amino)-4-methylpentanamido)-5-methyl-6-phenylhex-3-enoate ((R)-10b).: Obtained as an off-white, amorphous solid (1.20 g, 63% yield over two steps) after deprotection of compound **7** to afford compound **S1** (General Procedure B), which was immediately coupled with Boc-*D*-leucine (General Procedure C). $[\alpha]_D^{23} +46$ (c 15.9, CHCl_3); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) 5:1 mixture of Boc rotamers. Major rotamer: δ 8.03 (br d, $J = 9.4$ Hz, 1H), 7.29–7.14 (m, 5H), 6.9 (br d, $J = 8.6$ Hz, 1H), 5.36 (dd, $J = 6.0, 15.2$ Hz, 1H), 5.31 (dd, $J = 6.0, 15.2$ Hz, 1H), 4.69 (t, $J = 8.4$ Hz, 1H), 3.98 (dt, $J = 5.8, 9.0$ Hz, 1H), 3.51 (s, 3H), 2.92 (dd, $J = 6.6, 16.8$ Hz, 1H), 2.86 (dd, $J = 6.0, 16.8$ Hz, 1H), 2.60–2.50 (m, 1H), 1.55–1.41 (m, 1H), 1.36 (s, 9H), 1.35–1.26 (m, 2H), 0.93 (d, $J = 7.0$ Hz, 3H), 0.81 (d, $J = 6.6$ Hz, 3H), 0.77 (d, $J = 6.3$ Hz, 3H); Minor rotamer: δ 8.16 (br d, $J = 9.0$ Hz, 1H), 7.29–7.14 (m, 5H), 6.90–6.85 (m, 1H), 5.27–5.26 (m, 2H), 4.62 (t, $J = 9.0$ Hz, 1H), 4.03–3.93 (m, 1H), 3.51 (s, 3H), 2.89–2.82 (m, 1H), 2.65 (dd, $J = 5.9, 17.6$ Hz, 1H), 2.60–2.50 (m, 1H), 1.55–1.41 (m, 1H), 1.36 (s, 9H), 1.35–1.26 (m, 2H), 0.95–0.90 (m, 3H), 0.85–0.75 (m, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{DMSO}-d_6$, mixture of rotamers, all peaks reported) δ 171.8, 171.4, 171.3, 155.3, 141.7, 136.0, 135.3, 127.8, 127.7, 127.1, 127.0, 126.5, 122.2, 120.9, 77.9, 56.7, 56.5, 53.1, 51.4, 51.3, 41.4, 40.5, 37.1, 32.1, 28.1, 24.2, 22.8, 21.7, 17.2, 16.2; HRMS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{25}\text{H}_{38}\text{N}_2\text{O}_5\text{Na}$, 469.2678; found, 469.2670. IR (thin film): 3275, 1738, 1681, 1646, 753, 698 cm^{-1} .

Methyl (5S,6R,E)-6-((S)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)-5-methyl-6-phenylhex-3-enoate ((S)-10c).: Obtained as a pale yellow solid (386 mg, 83% yield over two steps) after deprotection of compound **7** to afford compound **S1** (General Procedure B), which was immediately coupled with Boc-*L*-valine (General Procedure C). mp 107–111 $^\circ\text{C}$; $[\alpha]_D^{23} +183$ (c 1.65, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 6.5:1 mixture of Boc rotamers. Major rotamer: δ 7.31–7.13 (m, 5H), 6.78 (br d, $J = 7.8$ Hz, 1H), 5.57 (dtd, $J = 1.2, 7.0, 15.6$ Hz, 1H), 5.37–5.25 (m, 1H), 5.18 (br d, $J = 7.8$ Hz, 1H), 4.91 (dd, $J = 5.5, 8.6$ Hz, 1H), 3.94 (dd, $J = 6.3, 8.6$ Hz, 1H), 3.71 (s, 3H), 3.07–3.02 (m, 2H), 2.59 (q, $J = 7.0$ Hz, 1H), 2.18–2.10 (m, 1H), 1.42 (s, 9H), 0.93 (d, $J = 6.6$ Hz, 6H), 0.88 (d, $J = 7.0$ Hz, 3H); Minor rotamer: δ 7.31–7.13 (m, 5H), 6.99 (br d, $J = 6.3$ Hz, 1H), 5.61–5.49 (m, 1H), 5.37–5.25 (m, 1H), 5.02 (br d, $J = 8.2$ Hz, 1H), 4.85 (dd, $J = 6.3, 8.2$ Hz, 1H), 3.95–3.86 (m, 1H), 3.70 (s, 3H), 3.01–2.97 (m, 2H), 2.92–2.80 (m, 1H), 2.12–2.05 (m, 1H), 1.40 (s, 9H), 0.98 (d, $J = 7.0$ Hz, 6H), 0.84 (d, $J = 7.0$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3 , mixture of

rotamers, all peaks reported) δ 172.6, 170.6, 155.8, 139.3, 136.0, 134.6, 128.0, 127.4, 127.1, 123.7, 121.9, 79.7, 60.1, 57.6, 56.7, 52.0, 47.8, 37.5, 32.8, 30.5, 28.3, 19.5, 17.6, 16.4; HRMS (m/z): $[M+Na]^+$ calcd. for $C_{24}H_{36}N_2O_5Na$, 455.2522, found, 455.2523. IR (thin film): 3399, 1741, 1686, 1645, 700, 636 cm^{-1} .

Methyl (5S,6R,E)-6-((R)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)-5-methyl-6-phenylhex-3-enoate ((R)-10c).: Obtained as a pale yellow solid (309 mg, 67% yield, two steps) after deprotection of compound **7** to compound **S1** (General Procedure B), which was immediately coupled with Boc-*D*-valine (General Procedure C). mp 72–75 °C; $[\alpha]_D^{23} +53$ (*c* 1.35, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) 6:1 mixture of Boc rotamers. Major rotamer: δ 7.31–7.12 (m, 5H), 6.77 (br d, *J* = 9.0 Hz, 1H), 5.56 (td, *J* = 7.2, 15.2 Hz, 1H), 5.30 (dd, *J* = 8.6, 15.2 Hz, 1H), 5.26–5.20 (m, 1H), 4.94 (dd, *J* = 5.9, 8.6 Hz, 1H), 3.93 (dd, *J* = 6.6, 8.6 Hz, 1H), 3.70 (s, 3H), 3.09–2.96 (m, 2H), 2.61 (sxt, *J* = 6.6 Hz, 1H), 2.22–2.08 (m, 1H), 1.44 (s, 9H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.89 (br d, *J* = 5.9 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H); Minor rotamer: δ 7.31–7.52 (m, 5H), 5.61–5.50 (m, 1H), 5.34–5.19 (m, 1H), 4.91–4.85 (m, 1H), 4.00 (dd, *J* = 5.9, 8.6 Hz, 1H), 3.74 (s, 3H), 3.09–2.96 (m, 2H), 2.92–2.82 (m, 1H), 2.22–2.08 (m, 1H), 1.44 (s, 9H), 0.98–0.95 (m, 3H), 0.92–0.89 (m, 3H), 0.79 (d, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, mixture of rotamers, all peaks reported) δ 172.6, 170.7, 156.0, 139.3, 135.6, 134.9, 128.1, 127.6, 127.4, 127.2, 124.0, 122.0, 79.6, 60.1, 59.4, 57.3, 56.7, 52.4, 52.0, 41.8, 37.4, 36.5, 32.8, 31.3, 28.3, 19.4, 18.0, 17.6, 16.6; HRMS (m/z): $[M+Na]^+$ calcd. for $C_{24}H_{36}N_2O_5Na$, 455.2522, found, 455.2525. IR (thin film): 3312, 1741, 1679, 1651, 702 cm^{-1} .

Methyl (5S,6R,E)-6-((S)-2-((tert-butoxycarbonyl)amino) propanamido)-5-methyl-6-phenylhex-3-enoate ((S)-10d).: Obtained as a white foam (202 mg, 69% yield, two steps) after deprotection of compound **7** to afford compound **S1** (General Procedure B), which was immediately coupled with Boc-*L*-alanine (General Procedure C). $[\alpha]_D^{23} +8$ (*c* 3.7, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) >10:1 mixture of Boc rotamers. Major rotamer reported. δ 7.29–7.11 (m, 5H), 7.03 (br d, *J* = 8.8 Hz, 1H), 5.54 (dtd, *J* = 0.8, 7.4, 15.6 Hz, 1H), 5.31 (dd, *J* = 8.0, 15.6 Hz, 1H), 5.10 (br d, *J* = 7.8 Hz, 1H), 4.87 (dd, *J* = 5.6, 8.8 Hz, 1H), 4.24–4.13 (m, 1H), 3.68 (s, 3H), 3.02 (d, *J* = 7.4 Hz, 2H), 2.59 (dq, *J* = 5.6, 6.6, 8.0 Hz, 1H), 1.42 (s, 9H), 1.32 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.5, 171.6, 155.6, 139.6, 135.8, 128.1, 127.4, 127.1, 123.6, 80.0, 56.8, 52.0, 50.0, 41.8, 37.6, 28.3, 17.9, 16.4; HRMS (m/z): $[M+Na]^+$ calcd. for $C_{22}H_{32}N_2O_5Na$, 427.2209; found, 427.2215. IR (thin film): 3321, 1737, 1712, 1662, 737, 702 cm^{-1} .

Methyl (5S,6R,E)-6-((R)-2-((tert-butoxycarbonyl)amino) propanamido)-5-methyl-6-phenylhex-3-enoate ((R)-10d).: Obtained as an orange oil (222 mg, 75% yield, two steps) after deprotection of compound **7** to afford compound **S1** (General Procedure B), which was immediately coupled with Boc-*D*-alanine (General Procedure C). $[\alpha]_D^{23} +3$ (*c* 4.45, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) >10:1 mixture of Boc rotamers. Major rotamer reported. δ 7.31–7.12 (m, 5H), 6.99 (br d, *J* = 8.2 Hz, 1H), 5.51 (dtd, *J* = 0.8, 7.4, 15.6 Hz, 1H), 5.36–5.28 (m, 1H), 5.32 (dd, *J* = 7.8, 15.6 Hz, 1H), 4.51 (dd, *J* = 6.0, 8.4 Hz, 1H), 4.25–4.12 (m, 1H), 3.67 (s, 3H), 3.02–2.98 (m, 2H), 2.61 (qdd, *J* = 6.6, 7.4, 8.4 Hz, 1H), 1.43 (br s, 9H), 1.30 (br d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100

MHz, CDCl₃, mixture of rotamers, all peaks reported) δ 172.7, 171.8, 155.7, 139.6, 134.7, 128.3, 128.2, 127.3, 127.1, 123.5, 121.9, 79.9, 57.2, 56.6, 52.2, 51.9, 50.1, 41.7, 37.4, 36.7, 32.9, 28.3, 17.9, 16.1; HRMS (m/z): [M+Na]⁺ calcd. for C₂₂H₃₂N₂O₅Na, 427.2209; found, 427.2204. IR (thin film): 3310, 1652, 1518 752, 700 cm⁻¹.

Methyl (5S,6R,E)-6-(3-bromophenyl)-6-((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-5-methylhex-3-enoate ((S)-10e).: Obtained as a colorless foam (1.26 g, 91% yield, two steps) after deprotection of compound **8** to compound **S2** (General Procedure B), which was immediately coupled with Boc-*L*-phenylalanine (General Procedure C). $[\alpha]_D^{23} +41$ (c 4.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.32 (br d, *J* = 7.8 Hz, 1H), 7.25–7.19 (m, 4H), 7.15 (br d, *J* = 6.6 Hz, 2H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.78 (br d, *J* = 8.2 Hz, 1H), 5.26 (dd, *J* = 7.0, 15.6 Hz, 1H), 5.21 (d, *J* = 8.2 Hz, 1H), 5.10 (dd, *J* = 9.0, 15.6 Hz, 1H), 4.73 (br dd, *J* = 5.5, 8.2 Hz, 1H), 4.38 (ddd, *J* = 6.0, 7.5, 8.2 Hz, 1H), 3.66 (s, 3H), 3.05 (dd, *J* = 6.0, 13.5 Hz, 1H), 2.98 (dd, *J* = 7.5, 13.5 Hz, 1H), 2.94 (d, *J* = 7.0 Hz, 2H), 2.32 (dq, *J* = 5.5, 6.5, 9.0 Hz, 1H), 1.38 (s, 9H), 0.83 (br d, *J* = 6.5 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 172.1, 170.3, 155.3, 141.8, 136.6, 135.0, 130.3, 130.1, 129.5, 129.2, 128.5, 126.7, 126.1, 124.0, 122.1, 79.9, 56.4, 55.8, 51.9, 41.4, 38.1, 37.2, 28.1, 16.4. HRMS (m/z): calcd. for, C₂₈H₃₅BrN₂O₅Na 581.1627; found, 581.1616. IR (thin film): 3311, 1702, 1658, 779, 699 cm⁻¹.

Methyl (5S,6R,E)-6-(3-bromophenyl)-6-((R)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-5-methylhex-3-enoate ((R)-10e).: Obtained as a colorless foam (420 mg, 75% yield, two steps) after deprotection of compound **8** to compound **S2** (General Procedure B), which was immediately coupled with Boc-*D*-phenylalanine (General Procedure C). $[\alpha]_D^{23} +74$ (c 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, *J* = 7.8 Hz, 1H), 7.24–7.18 (m, 2H), 7.18–7.07 (m, 6H), 6.94 (br d, *J* = 7.4 Hz, 1H), 6.87 (br d, *J* = 7.4 Hz, 1H), 5.44 (br d, *J* = 9.0 Hz, 1H), 5.39 (td, *J* = 7.0, 15.6 Hz, 1H), 5.22 (dd, *J* = 8.2, 15.6 Hz, 1H), 4.82 (br dd, *J* = 6.6, 9.0 Hz, 1H), 4.39 (t, *J* = 7.4 Hz, 1H), 3.66 (s, 3H), 2.99 (br d, *J* = 7.4 Hz, 2H), 2.95 (d, *J* = 7.0 Hz, 2H), 2.50 (qd, *J* = 6.6, 8.2 Hz, 1H), 1.39 (br s, 9H), 0.89 (d, *J* = 6.6 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 172.2, 170.5, 155.4, 141.9, 136.5, 134.9, 130.2, 130.1, 129.5, 129.1, 128.3, 126.6, 125.9, 123.8, 122.1, 79.7, 56.4, 55.8, 51.8, 41.4, 38.0, 37.2, 28.1, 16.1. HRMS (m/z): calcd. for C₂₈H₃₅BrN₂O₅Na 581.1627; found, 581.1605. IR (thin film): 3318, 1686, 1650, 701 cm⁻¹.

Methyl (5S,6S,E)-6-((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-6-cyclopropyl-5-methylhex-3-enoate ((S)-10f).: Obtained as a pale yellow gum (639 mg, 95% yield, two steps) after deprotection of compound **9** to compound **S3** (General Procedure B), which was immediately coupled with Boc-*L*-phenylalanine (General Procedure C). $[\alpha]_D^{23} -36$ (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.23 (m, 5H), 6.33 (br d, *J* = 9.4 Hz, 1H), 5.50–5.39 (m, 2H), 5.29 (td, *J* = 7.2, 15.0 Hz, 1H), 4.39 (br q, *J* = 7.0 Hz, 1H), 3.74 (s, 3H), 3.39–3.29 (m, 1H), 3.08 (br d, *J* = 5.5 Hz, 2H), 3.04 (d, *J* = 7.0 Hz, 2H), 2.28 (br q, *J* = 6.3 Hz, 1H), 1.47 (s, 9H), 1.04 (br d, *J* = 6.3 Hz, 3H), 0.76 (dtd, *J* = 5.1, 8.6, 13.3 Hz, 1H), 0.56 (t, *J* = 8.2 Hz, 1H), 0.43–0.26 (m, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 172.2, 170.4, 155.2, 136.7, 135.9, 129.2, 128.3, 126.6, 122.7, 121.2, 79.6, 56.7, 56.1, 51.6, 41.6, 38.3, 37.4, 32.7, 28.1, 16.6, 12.2, 4.7, 1.4; HRMS (m/z): calcd. for

$C_{25}H_{36}N_2O_5Na$, 467.2522; found, 467.2532. IR (thin film): 3309, 1740, 1686, 1651, 699 cm^{-1} .

Methyl (5S,6S,E)-6-((R)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-6-cyclopropyl-5-methylhex-3-enoate ((R)-10f).: Obtained as a pale yellow solid (522 mg, 70% yield, two steps) after deprotection of compound **9** to compound **S3** (General Procedure B), which was immediately coupled with Boc-*D*-phenylalanine (General Procedure C). mp 121–124 °C; $[\alpha]^{23}_D +9$ (*c* 1.0, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.15 (m, 5H), 6.11 (br d, *J* = 7.4 Hz, 1H), 5.46–5.38 (m, 2H), 5.32 (td, *J* = 6.6, 15.2 Hz, 1H), 4.33 (br q, *J* = 7.0 Hz, 1H), 3.65 (s, 3H), 3.23–3.14 (m, 1H), 3.05–3.00 (m, 1H), 2.99–2.95 (m, 3H), 2.45–2.30 (m, 1H), 1.40–1.34 (m, 9H), 1.01 (br d, *J* = 7.0 Hz, 3H), 0.69–0.55 (m, 1H), 0.46 (br s, 1H), 0.32–0.12 (m, 2H), 0.06 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.5, 170.8, 170.2, 155.3, 136.8, 135.8, 135.5, 129.3, 129.2, 128.4, 128.3, 126.5, 122.9, 79.5, 57.0, 56.96, 55.9, 51.6, 41.6, 38.2, 37.4, 37.3, 36.8, 28.1, 16.5, 16.2, 11.9, 4.8, 1.6; HRMS (*m/z*): calcd. for $C_{25}H_{36}N_2O_5Na$, 467.2522; found, 467.2521. IR (thin film): 3338, 1737, 1684, 1649, 753, 697 cm^{-1} .

tert-Butyl (S)-2-(((1R,2S,E)-6-methoxy-2-methyl-6-oxo-1-phenylhex-3-en-1-yl)carbamoyl)pyrrolidine-1-carboxylate ((S)-10g).: Obtained as a yellow oil (268 mg, 73% yield, two steps) after deprotection of compound **7** to compound **S1** (General Procedure B), which was immediately coupled with Boc-*L*-proline (General Procedure C). 1H NMR in $CDCl_3$ indicated an approximate 9:1 ratio of Boc rotamers with significant broadening and peak overlap; major signals are reported. $[\alpha]^{23}_D +26$ (*c* 7.75, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) Major rotamer: δ 7.30–7.15 (m, 5H), 5.60–5.47 (m, 1H), 5.40–5.25 (m, 1H), 4.89 (dd, *J* = 5.9, 9.0 Hz, 1H), 4.40–4.30 (br. m, 1H), 3.66 (s, 3H), 3.54–3.22 (br m, 3H), 3.0 (br. s, 2H), 2.65–2.51 (m, 1H), 1.90–1.75 (br. m, 3H), 1.47 (br. s, 9H), 0.98 (br. s, 3H); Minor rotamer: δ 7.30–7.15 (m, 5H), 5.60–5.47 (m 1H), 5.40–5.25 (m, 1H), 4.84 (dd, *J* = 9.4, 7.4 Hz, 1H), 4.30–4.20 (br. m, 1H), 3.64 (s, 3H), 3.54–3.22 (br m, 1H), 2.90–2.75 (m, 2H), 2.65–2.51 (m, 1H), 2.45–2.32 (br. m, 3H), 1.47 (br. s, 9H), 0.98 (br. s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, mixture of rotamers, all peaks reported) δ 172.0, 171.8, 156.0, 154.6, 140.3, 135.5, 127.9, 127.1, 126.7, 122.9, 121.7, 80.2, 60.2, 59.5, 56.9, 46.9, 42.0, 37.6, 32.7, 28.8, 28.2, 28.0, 27.2, 24.4, 23.5, 17.0, 15.8, 14.0; HRMS (*m/z*): $[M+Na]^+$ calcd. for $C_{24}H_{34}N_2O_5Na$, 453.2365; found, 453.2370; IR (thin film): 3309, 1738, 1659, 753, 701 cm^{-1} .

tert-Butyl (R)-2-(((1R,2S,E)-6-methoxy-2-methyl-6-oxo-1-phenylhex-3-en-1-yl)carbamoyl)pyrrolidine-1-carboxylate ((R)-10g).: Obtained as an orange oil (372 mg, 67% yield, two steps) after deprotection of compound **15** to compound **S1** (General Procedure B), which was immediately coupled with Boc-*D*-proline (General Procedure C). 1H NMR in $DMSO-d_6$ indicated an approximately 1.7:1 mixture of Boc rotamers with significant broadening and peak overlap; signals for the major identified rotamer are reported. $[\alpha]^{23}_D +99$ (*c* 1.75, $CHCl_3$); 1H NMR (400 MHz, $DMSO-d_6$) δ 8.06 (d, *J* = 9.0 Hz, 1H), 7.30–7.15 (m, 5H), 5.45–5.21 (m, 2H), 4.75–4.57 (m, 1H), 4.20–4.10 (m, 1H), 3.53 (s, 3H), 3.40–3.30 (m, 1H) 3.30–3.22 (m, 1H), 3.00–2.85 (m, 2H), 2.70–2.55 (m, 1H), 2.17–2.07 (m, 1H), 1.80–1.60 (m, 3H), 1.25 (s, 9H), 1.00–0.90 (m, 3H). $^{13}C\{^1H\}$ NMR (100

MHz, DMSO- d_6 , mixture of rotamers, all peaks reported) δ 171.5, 171.4, 153.7, 153.4, 142.1, 141.7, 136.2, 127.8, 127.2, 126.6, 122.2, 78.6, 78.3, 59.7, 59.4, 57.1, 56.5, 51.4, 46.7, 46.6, 41.5, 41.1, 37.1, 31.1, 29.6, 28.1, 28.0, 24.0, 23.0, 16.9, 16.2; HRMS (m/z): $[M+Na]^+$ calcd. for $C_{24}H_{34}N_2O_5Na$, 453.2365; found, 453.2376; IR (thin film): 3312, 1739, 1696, cm^{-1} .

General Procedure D: Boc deprotection. Compound **10** was dissolved in CH_2Cl_2 to give a 0.2 M solution. The solution was transferred to a microwave vessel. SCX resin (1.5 equiv, 0.54 mmol/g) was added in one portion and the reaction was subjected to microwave irradiation (300W maximum wattage, 100 °C maximum temperature, 250 psi maximum pressure) for 10 minutes. The vessel was allowed to cool to room temperature before opening, and the resin was isolated by filtration, rinsing with three portions of dichloromethane. The resin was return to the cleaned microwave vessel and a solution of 3:1 $CH_2Cl_2:Et_3N$ was added. The vessel was subjected to microwave irradiation (300W maximum wattage, 60 °C maximum temperature, 250 psi maximum pressure) for three minutes to release the deprotected amine. The vessel was then cooled to room temperature and the resin was filtered from the solution, rinsing with three portions of dichloromethane. The mother liquor was condensed to give the crude deprotected product **1** which was carried on to the cyclization step without further purification.

General Procedure E: DBU-mediated cyclization. The crude amine **1a-g** from the Boc deprotection step was dissolved in acetonitrile to give an 0.1M solution. DBU (2.0 equiv) was added and the reaction was heated to 90 °C for three hours. Upon completion as indicated by LC/MS, the reaction mixture was directly applied to a short column of silica (1 cm diameter, maximum length 3 cm) wetted with 5% acetone in hexanes. The product was eluted with 50 mL portions of the following gradient: 5%, 10%, 20%, 30%, 40%, 50%, 60%, 80% acetone in hexanes.

General Procedure F: Sodium methoxide-mediated cyclization. The crude amine **1a-g** from the Boc deprotection step (1.0 equiv) was dissolved in anhydrous DMF at room temperature (0.1 M concentration). A solution of sodium methoxide in methanol (25% w/w, 2.0 equiv) was added in one portion and the reaction was stirred at room temperature for 30 minutes. When LC/MS indicated reaction completion, the solution was diluted with 50 volume equivalents of ethyl acetate, washed with 6 portions of water (2 mL water per 1 mL original reaction volume), and washed once with brine. The organic fraction was dried over sodium sulfate and condensed to give a crude residue. The residue was applied to a short column of silica (1 cm diameter, maximum length 3 cm) wetted with 5% acetone in hexanes. The product was eluted with 50 mL portions of the following gradient: 5%, 10%, 20%, 30%, 40%, 50%, 60%, 80% acetone in hexanes.

(4S,7R,8S,9aS)-4-Benzyl-8-methyl-7-phenylhexahydro-1H-pyrrolo[1,2-d]

[1,4]diazepine-2,5-dione ((S,S)-3a): Obtained as a white solid from compound (*S*)-**10a** after deprotection (General Procedure D) to afford (*S*)-**1a** followed by cyclization using General Procedure E (64 mg, 81% yield, 6:1 d.r., 1H NMR chemical shifts for minor diastereomer appear to correlate to compound (*R,R*)-**3a**). Also obtained as major product

when compound (*S*)-**1a** was subjected to cyclization using General Procedure F (56 mg, 72% yield, 13:1 d.r.). mp = 172–175 °C; $[\alpha]_D^{23}$ –56 (*c* 1.05, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.28 (m, 4H), 7.27–7.21 (m, 4H), 7.13–7.09 (m, 2H), 5.78 (br. d, *J* = 3.5 Hz, 1H), 5.18 (d, *J* = 8.2 Hz, 1H), 4.42 (ddd, *J* = 3.5, 5.3, 9.0 Hz, 1H), 4.28 (dddd, *J* = 5.0, 6.3, 10.0, 10.5 Hz, 1H), 3.33 (dd, *J* = 5.3, 14.5 Hz, 1H), 3.04 (dd, *J* = 5.1, 17.6 Hz, 1H), 2.81 (dd, *J* = 10.5, 17.5 Hz, 1H), 2.84 (dd, *J* = 9.0, 14.5 Hz, 1H), 2.50 (qdd, *J* = 6.6, 8.0, 13.4 Hz, 1H), 2.29 (td, *J* = 6.3, 12.5 Hz, 1H), 1.55 (ddd, *J* = 10.0, 12.5, 13.4 Hz, 1H), 0.67 (d, *J* = 6.6 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 171.1, 169.0, 138.2, 136.3, 129.3, 128.8, 128.2, 126.9, 66.2, 54.8, 52.9, 42.0, 40.8, 36.5, 36.1, 14.8; HRMS (*m/z*): [M+H]⁺ calcd. for C₂₂H₂₅N₂O₂, 349.1916; found, 349.1906. IR (thin film): 3260, 1667, 1639, 742, 696 cm^{–1}.

(4R,7R,8S,9aR)-4-Benzyl-8-methyl-7-phenylhexahydro-1H-pyrrolo[1,2-d]

[1,4]diazepine-2,5-dione ((R,R)-3a).: Obtained as a clear oil from compound (*R*)-**10a** after deprotection (General Procedure D) to afford (*R*)-**1a** followed by cyclization using General Procedure F (45 mg, 98% yield, 7.5:1 d.r., ¹H NMR chemical shifts for minor diastereomer appear to correlate to compound (*S,S*)-**3a**). $[\alpha]_D^{23}$ +12.5 (*c* 0.08, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.20 (m, 8H), 7.08 (d, *J* = 7.0 Hz, 2H), 5.60 (br. s., 1H), 5.18 (d, *J* = 8.2 Hz, 1H), 4.68–4.61 (m, 1H), 4.57 (ddd, *J* = 2.7, 4.5, 10.0 Hz, 1H), 3.30 (dd, *J* = 4.5, 15.0 Hz, 1H), 2.82 (dd, *J* = 10.0, 15.0 Hz, 1H), 2.77–2.64 (m, 3H), 2.12 (dt, *J* = 8.4, 13.0 Hz, 1H), 1.74 (dd, *J* = 6.1, 13.1 Hz, 1H), 0.67 (d, *J* = 7.0 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 170.8, 167.3, 138.4, 135.9, 129.2, 129.1, 128.3, 127.4, 127.3, 126.5, 65.4, 54.5, 52.5, 42.7, 37.4, 36.3, 34.4, 14.8; HRMS (*m/z*): [M+H]⁺ calcd. for C₂₂H₂₅N₂O₂, 349.1916; found, 349.1915; IR (thin film) 3205, 1656, 796, 747, 702 cm^{–1}.

(4S,7R,8S,9aS)-4-Isobutyl-8-methyl-7-phenylhexahydro-1H-pyrrolo[1,2-d]

[1,4]diazepine-2,5-dione ((S,S)-3b).: Obtained as a white solid from compound (*S*)-**10b** after deprotection (General Procedure D) to afford (*S*)-**1b** followed by cyclization using General Procedure E (81 mg, 81% yield, 17:1 d.r., ¹H NMR chemical shifts for minor diastereomer appear to correlate to compound (*R,R*)-**3b**). Also obtained as major product when compound (*S*)-**1b** was subjected to cyclization using General Procedure F (46 mg, 65% yield, 3:1 d.r.). mp = 160–163 °C; $[\alpha]_D^{23}$ +520 (*c* 0.94, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.28 (m, 2H), 7.26–7.21 (m, 1H), 7.11 (d, *J* = 7.1 Hz, 2H), 5.64 (br. d, *J* = 4.7 Hz, 1H), 5.18 (d, *J* = 8.2 Hz, 1H), 4.32 (dddd, *J* = 5.9, 6.3, 9.8, 10.0 Hz, 1H), 4.19 (ddd, *J* = 4.7, 5.1, 8.6 Hz, 1H), 3.17 (dd, *J* = 5.9, 17.2 Hz, 1H), 2.91 (dd, *J* = 9.8, 17.2 Hz, 1H), 2.53 (dqdd, *J* = 6.3, 7.0, 8.2, 12.9 Hz, 1H), 2.34 (td, *J* = 6.3, 12.5 Hz, 1H), 1.84 (ddd, *J* = 5.8, 8.6, 14.3 Hz, 1H), 1.73 (dqdd, *J* = 5.8, 6.3, 6.6, 8.6 Hz, 1H), 1.61 (ddd, *J* = 10.0, 12.5, 12.9 Hz, 1H), 1.47 (ddd, *J* = 4.7, 8.6, 14.3 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.3 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 171.1, 169.8, 138.3, 128.3, 127.2, 126.9, 65.9, 53.1, 51.3, 42.0, 41.3, 39.0, 36.2, 24.4, 23.0, 21.9, 14.9; HRMS (*m/z*): [M+H]⁺ calcd. for C₁₉H₂₇N₂O₂, 315.2073; found, 315.2076. IR (thin film) 3209, 1658, 805, 744, 701 cm^{–1}.

(4R,7R,8S,9aR)-4-Isobutyl-8-methyl-7-phenylhexahydro-1H-pyrrolo[1,2-d]

[1,4]diazepine-2,5-dione ((R,R)-3b).: Obtained as a pale yellow oil from compound (*R*)-**10b** after deprotection (General Procedure D) to afford (*R*)-**1b** followed by cyclization

using General Procedure F (21 mg, 94% yield, 7:1 d.r., ^1H NMR chemical shifts for minor diastereomer appear to correlate to compound (*S,S*)-**3b**). $[\alpha]^{23}_{\text{D}} +182$ (*c* 0.69, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.28 (m, $J = 7.8$ Hz, 3H), 7.05 (d, $J = 7.4$ Hz, 2H), 5.58 (s, 1H), 5.14 (d, $J = 7.8$ Hz, 1H), 4.68 (ddd, $J = 3.9, 8.3, 12.1$ Hz, 1H), 4.34 (ddd, $J = 3.0, 6.3, 7.7$ Hz, 1H), 2.85 (dd, $J = 3.9, 18.0$ Hz, 1H), 2.74 (dd, $J = 12.1, 18.0$ Hz, 1H), 2.80–2.65 (m, 1H), 2.11 (dt, $J = 8.3, 13.0$ Hz, 1H), 1.85 (ddd, $J = 6.3, 7.9, 14.0$ Hz, 1H), 1.74–1.63 (m, 1H), 1.65–1.55 (m, 1H), 1.41 (ddd, $J = 6.4, 7.7, 14.0$ Hz, 1H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.91 (d, $J = 6.6$ Hz, 3H), 0.66 (d, $J = 6.6$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 171.0, 167.8, 138.6, 128.3, 127.3, 126.5, 65.2, 52.7, 51.4, 42.6, 39.1, 37.4, 34.4, 24.4, 22.7, 22.0, 14.8; HRMS (*m/z*): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_2$, 315.2073; found, 315.2058. IR (thin film) cm^{-1} .

(4*S*,7*R*,8*S*,9*aS*)-4-Isopropyl-8-methyl-7-phenylhexahydro-1*H*-pyrrolo[1,2-*d*]

[1,4]diazepine-2,5-dione ((*S,S*)-3c**).** Obtained as an amorphous pale yellow solid from compound (*S*)-**10c** after deprotection (General Procedure D) to afford (*S*)-**1c** followed by cyclization using General Procedure E (50 mg, 72% yield of a single diastereomer after chromatography). $[\alpha]^{23}_{\text{D}} +131$ (*c* 1.3, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.30–7.23 (m, 2H), 7.21–7.14 (m, 1H), 7.09–7.02 (m, 2H), 5.89 (br d, $J = 5.9$ Hz, 1H), 5.12 (d, $J = 8.2$ Hz, 1H), 4.24 (tdd, $J = 6.3, 9.0, 10.8$ Hz, 1H), 3.80 (dd, $J = 5.9, 7.0$ Hz, 1H), 3.12 (dd, $J = 6.3, 17.2$ Hz, 1H), 2.86 (dd, $J = 9.0, 17.2$ Hz, 1H), 2.46 (sptd, $J = 6.6, 7.0$ Hz, 1H), 2.27 (dd, $J = 6.3, 12.8$ Hz, 1H), 2.23 (qdd, $J = 7.0, 8.2, 12.8$ Hz, 1H), 1.57 (dt, $J = 10.8, 12.8$ Hz, 1H), 0.99 (t, $J = 6.6$ Hz, 1H), 1.06–0.92 (m, 5H), 0.62 (d, $J = 7.0$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 171.7, 169.3, 138.6, 128.3, 127.1, 126.9, 65.8, 58.9, 53.2, 41.9, 41.3, 36.1, 28.1, 20.4, 18.0, 14.9; HRMS (*m/z*): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_2$, 301.1916; found, 301.1912. IR (thin film) 2961, 1659, 748 cm^{-1} .

(4*R*,7*R*,8*S*,9*aR*)-4-Isopropyl-8-methyl-7-phenylhexahydro-1*H*-pyrrolo[1,2-*d*]

[1,4]diazepine-2,5-dione ((*R,R*)-3c**).** Obtained as a clear oil from compound (*R*)-**10c** after deprotection (General Procedure D) to (*R*)-**1c** followed by cyclization using General Procedure F (16 mg, 91% yield of a single diastereomer after chromatography). $[\alpha]^{23}_{\text{D}} -285$ (*c* 0.19, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.22 (m, 3H), 7.09–7.02 (m, 2H), 5.78 (br s, 1H), 5.15 (d, $J = 7.8$ Hz, 1H), 4.67 (ddd, $J = 4.3, 8.1, 12.2$ Hz, 1H), 4.03 (dd, $J = 3.9, 7.0$ Hz, 1H), 2.86 (dd, $J = 4.3, 18.4$ Hz, 1H), 2.73 (dd, $J = 12.2, 18.4$ Hz, 1H), 2.70 (dqdd, $J = 6.0, 6.6, 7.8, 13.1$ Hz, 1H), 2.27–2.17 (m, 1H), 2.09 (dt, $J = 8.2, 13.1$ Hz, 1H), 1.73 (dd, $J = 6.0, 12.7$ Hz, 1H), 1.06 (d, $J = 6.6$ Hz, 3H), 0.98 (d, $J = 6.6$ Hz, 3H), 0.67 (d, $J = 6.6$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 171.2, 167.7, 138.6, 128.3, 127.2, 65.0, 58.7, 52.7, 42.6, 37.5, 34.4, 27.8, 20.2, 17.7, 14.9; HRMS (*m/z*): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_2$, 301.1916; found, 301.1911. IR (thin film) 1653, 744 cm^{-1} .

(4*S*,7*R*,8*S*,9*aS*)-4,8-Dimethyl-7-phenylhexahydro-1*H*-pyrrolo[1,2-*d*][1,4]diazepine-2,5-dione ((*S,S*)-3d**).**

Obtained as a clear oil from compound (*S*)-**10d** after deprotection (General Procedure D) to (*S*)-**1d** followed by cyclization using General Procedure E (39 mg, 58% yield, 12:1 d.r., ^1H NMR chemical shifts of minor diastereomer do not appear to match (*R,R*)-**3d**). $[\alpha]^{23}_{\text{D}} +311$ (*c* 0.16, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.28 (m, 2H), 7.26–7.21 (m, 1H), 7.11 (d, $J = 7.4$ Hz, 2H), 6.01 (br d, $J = 4.0$ Hz, 1H), 5.19 (d, $J = 8.2$ Hz,

1H), 4.34 (dq, $J = 4.0, 6.6$ Hz, 1H), 4.30 (dddd, $J = 5.3, 6.3, 10.0, 10.6$ Hz, 1H), 3.13 (dd, $J = 5.3, 17.8$ Hz, 1H), 2.89 (dd, $J = 10.6, 17.8$ Hz, 1H), 2.51 (dqdd, $J = 6.3, 6.6, 8.2, 12.8$ Hz, 1H), 2.34 (td, $J = 6.3, 12.8$ Hz, 1H), 1.57 (dt, $J = 10.0, 12.8$ Hz, 1H), 1.38 (d, $J = 6.6$ Hz, 3H), 0.69 (d, $J = 6.6$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 171.0, 170.0, 135.2, 128.3, 127.2, 127.0, 66.0, 52.9, 48.8, 42.1, 41.0, 36.3, 16.0, 14.9; HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_2$, 273.1603; found, 273.1602. IR (thin film) 3220, 1653, 735 cm^{-1} .

(4R,7R,8S,9aR)-4,8-Dimethyl-7-phenylhexahydro-1H-pyrrolo[1,2-d][1,4]diazepine-2,5-dione ((R,R)-3d). Obtained as a clear oil from compound (*R*)-10d after deprotection (General Procedure D) to afford (*R*)-1d followed by cyclization using General Procedure F (38 mg, 56% yield, 9:1 d.r., ^1H NMR chemical shifts of minor diastereomer appear to match (*S,S*)-3d). $[\alpha]_D^{23} +27$ (c 0.87, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.22 (m, 3H), 7.04 (d, $J = 7.4$ Hz, 2H), 6.18 (br. s., 1H), 5.12 (d, $J = 8.2$ Hz, 1H), 4.61 (ddd, $J = 4.3, 8.2, 11.9$ Hz, 1H), 4.45 (dq, $J = 2.7, 6.6$ Hz, 1H), 2.80–2.65 (m, 3H), 2.09 (dt, $J = 8.2, 13.1$ Hz, 1H), 1.71 (dd, $J = 6.3, 13.1$ Hz, 1H), 1.32 (d, $J = 6.6$ Hz, 3H), 0.64 (d, $J = 6.6$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 171.2, 168.0, 138.6, 128.3, 127.3, 126.5, 65.4, 52.5, 49.2, 42.6, 37.4, 34.4, 16.3, 14.8; HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_2$, 273.1603; found, 273.1602. IR (thin film) 1654, 749, 701 cm^{-1} .

(4S,7R,8S,9aS)-4-Benzyl-7-(3-bromophenyl)-8-methylhexahydro-1H-pyrrolo[1,2-d][1,4]diazepine-2,5-dione ((S,S)-3e). Obtained as a white foam from compound (*S*)-10e after deprotection (General Procedure D) to (*S*)-1e followed by cyclization using General Procedure E. ^1H NMR analysis of the crude isolate suggested an initial 4.3:1 d.r.; the chemical shifts of the observed minor diastereomer did not match (*R,R*)-2e and are presumed to be another, undetermined diastereomer. After chromatography, (*S,S*)-3e was isolated as a single diastereomer in 74% yield (69 mg). $[\alpha]_D^{23} -1.9$ (c 3.3, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.39 (dd, $J = 1.2, 7.4$ Hz, 1H), 7.35–7.30 (m, 2H), 7.29–7.17 (m, 5H), 7.03 (d, $J = 7.8$ Hz, 1H), 5.74 (d, $J = 4.3$ Hz, 1H), 5.12 (d, $J = 8.2$ Hz, 1H), 4.41 (ddd, $J = 4.3, 5.3, 9.0$ Hz, 1H), 4.27 (ddt, $J = 5.1, 6.2, 10.2$ Hz, 1H), 3.33 (dd, $J = 5.3, 14.7$ Hz, 1H), 3.05 (dd, $J = 5.1, 17.6$ Hz, 1H), 2.85 (dd, $J = 9.0, 14.7$ Hz, 1H), 2.77 (dd, $J = 10.2, 17.6$ Hz, 1H), 2.52 (dqdd, $J = 6.2, 7.0, 8.2, 12.7$ Hz, 1H), 2.31 (td, $J = 6.2, 12.7$ Hz, 1H), 1.55 (dt, $J = 10.2, 12.7$ Hz, 1H), 0.69 (d, $J = 7.0$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 171.1, 169.2, 140.9, 136.3, 136.0, 130.5, 130.4, 130.2, 129.9, 129.5, 129.3, 129.0, 128.9, 127.4, 127.2, 125.3, 122.5, 67.2, 65.7, 58.2, 55.2, 55.1, 53.1, 41.9, 40.9, 40.7, 39.3, 38.6, 36.6, 36.1, 35.1, 14.9; HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{22}\text{H}_{24}\text{BrN}_2\text{O}_2$, 427.1021; found, 427.1013. IR (thin film): 3211, 1653, 749, 700 cm^{-1} .

(4R,7R,8S,9aR)-4-Benzyl-7-(3-bromophenyl)-8-methylhexahydro-1H-pyrrolo[1,2-d][1,4]diazepine-2,5-dione ((R,R)-3e). Obtained as a clear oil from compound (*R*)-10e after deprotection (General Procedure D) to (*R*)-1e followed by cyclization using General Procedure E. ^1H NMR analysis of the crude isolate suggested an initial 3.2:1 d.r.; the chemical shifts of the observed minor diastereomer do not match (*S,S*)-3e and it is presumed to be another, unspecified diastereomer. After chromatography, (*R,R*)-3e was isolated as a single diastereomer in 68% yield (56 mg). $[\alpha]_D^{23} +5.5$ (c 2.15, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.45 (d, $J = 7.0$ Hz, 1H), 7.41–7.35 (m, 2H), 7.34–7.28 (m, 3H), 7.26–7.20

(m, 2H), 7.07 (d, $J = 7.8$ Hz, 1H), 5.95 (d, $J = 2.3$ Hz, 1H), 5.19 (d, $J = 8.2$ Hz, 1H), 4.68 (br ddd, $J = 6.0, 8.2, 9.8$ Hz, 1H), 4.62 (ddd, $J = 2.8, 5.1, 9.4$ Hz, 1H), 3.35 (dd, $J = 5.1, 14.9$ Hz, 1H), 2.88 (dd, $J = 9.4, 14.9$ Hz, 1H), 2.79 (qdd, $J = 6.6, 8.2, 13.0$ Hz, 1H), 2.80 (d, $J = 18.4$ Hz, 1H), 2.75 (dd, $J = 9.8, 18.4$ Hz, 1H), 2.11 (dt, $J = 8.4, 13.0$ Hz, 1H), 1.78 (dd, $J = 6.0, 13.0$ Hz, 1H), 0.73 (d, $J = 6.6$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (400 MHz, CDCl_3) δ 170.8, 167.5, 141.1, 136.1, 130.5, 129.8, 129.2, 129.1, 129.0, 127.2, 125.4, 122.6, 64.7, 54.5, 52.5, 42.4, 37.4, 36.0, 34.3, 14.8; HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{22}\text{H}_{24}\text{BrN}_2\text{O}_2$, 427.1021; found, 427.1014. IR (thin film): 3210, 1654, 750, 701 cm^{-1} .

(4S,7R,8S,9aS)-4-Benzyl-7-cyclopropyl-8-methylhexahydro-1H-pyrrolo[1,2-d]

[1,4]diazepine-2,5-dione ((S,S)-3f).: Obtained as a white solid from compound (*S*)-**10f** after deprotection (General Procedure D) to (*S*)-**1f** followed by cyclization using General Procedure E (31 mg, 68% yield as a single diastereomer after chromatography, ^1H NMR analysis of the crude isolate suggested a single diastereomer formed under the reaction conditions). Mp = 232–236 °C; $[\alpha]_D^{23}$ –22 (c 0.8, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.30 (m, 2H), 7.28–7.22 (m, 3H), 5.75 (br s, 1H), 4.43 (ddd, $J = 2.7, 4.9, 9.5$ Hz, 1H), 4.17 (dddd, $J = 3.5, 7.2, 9.0, 12.2$ Hz, 1H), 3.52 (dd, $J = 7.0, 10.2$ Hz, 1H), 3.38 (dd, $J = 4.9, 14.8$ Hz, 1H), 2.87 (dd, $J = 3.5, 18.3$ Hz, 1H), 2.84 (dd, $J = 9.5, 14.8$ Hz, 1H), 2.54 (dd, $J = 12.2, 18.3$ Hz, 1H), 2.38 (ddd, $J = 6.8, 7.4, 12.5$ Hz, 1H), 2.25 (dddq, $J = 6.6, 6.8, 7.0, 12.7$ Hz, 1H), 1.52 (dt, $J = 9.0, 12.7$ Hz, 1H), 1.15 (d, $J = 6.6$ Hz, 3H), 0.81–0.73 (m, 1H), 0.70–0.60 (m, 1H), 0.58–0.44 (m, 2H), 0.30–0.22 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 170.8, 168.5, 136.3, 129.2, 129.0, 127.2, 66.1, 54.1, 51.8, 43.8, 40.2, 36.5, 14.5, 14.4, 11.9, 3.9, 2.4; HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_2$, 313.1916, found 313.1915. IR (thin film): 3318, 1740, 1686, 1650 cm^{-1} .

(4R,7R,8S,9aR)-4-Benzyl-7-cyclopropyl-8-methylhexahydro-1H-pyrrolo[1,2-d]

[1,4]diazepine-2,5-dione ((R,R)-3f).: Obtained as a clear oil from compound (*R*)-**10f** after deprotection (General Procedure D) to afford (*R*)-**1f** followed by cyclization using General Procedure E (53 mg, 66% yield as a single diastereomer, ^1H NMR analysis of the crude isolate suggested an initial 4:1 d.r., with the chemical shifts of the minor isomer matching (*S,S*)-**3f**. $[\alpha]_D^{23}$ –24 (c 1.2, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.32–7.18 (m, 5H), 5.61 (br s, 1H), 4.42–4.40 (m, 1H), 4.40 (ddd, $J = 2.8, 5.3, 9.4$ Hz, 1H), 4.30 (ddd, $J = 4.3, 8.2, 11.6$ Hz, 1H), 3.55 (dd, $J = 7.4, 9.8$ Hz, 1H), 3.31 (dd, $J = 5.3, 14.7$ Hz, 1H), 2.81 (dd, $J = 9.4, 14.7$ Hz, 1H), 2.58 (dd, $J = 4.3, 18.0$ Hz, 1H), 2.50 (dd, $J = 11.6, 18.0$ Hz, 1H), 2.40 (dqdd, $J = 6.0, 6.6, 7.4, 12.9$ Hz, 1H), 2.06 (dt, $J = 8.2, 12.9$ Hz, 1H), 1.62 (dd, $J = 5.5, 12.9$ Hz, 1H), 1.11 (d, $J = 6.6$ Hz, 3H), 0.85–0.76 (m, 1H), 0.62–0.53 (m, 1H), 0.47–0.37 (m, 2H), 0.18–0.11 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 171.3, 168.3, 136.6, 129.6, 129.3, 127.5, 66.1, 55.0, 51.8, 43.3, 385.7, 36.9, 34.6, 14.9, 11.9, 3.8, 3.3; HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_2$, 313.1916; found, 313.1904. IR (thin film): 3206, 1651, 753, 701 cm^{-1} .

(2S,3R,5aS,11aS)-2-Methyl-3-phenyloctahydro-5H-dipyrrolo[1,2-a:1',2'-d]

[1,4]diazepine-5,10(1H)-dione ((5aS,11aS)-3g).: Obtained as the major diastereomeric product (amorphous white solid) from compound (*S*)-**10g** after deprotection (General Procedure D) to afford (*S*)-**1g** followed by cyclization using General Procedure E (52 mg,

75% yield, 14:1 d.r., ^1H NMR chemical shifts of minor diastereomer correlated with product (*5aR,11aR*)-**3g**). In addition, the major diastereomer obtained after treating (*S*)-**1g** under General Procedure F (31 mg, 61% yield, 14:1:1 d.r., ^1H NMR chemical shifts of minor diastereomers correlated with products (*5aR,11aR*)-**3g** and (*5aR,11aS*)-**3g**), and when treating compound (*5aR,11aS*)-**3g** under General Procedure F. The diastereomeric ratio was further enriched by repeated chromatography for 2D NMR characterization purposes. $[\alpha]^{23}_{\text{D}} -31$ (*c* 3.4, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.34–7.27 (m, 2H), 7.24 (d, *J* = 6.6 Hz, 1H), 7.10 (d, *J* = 7.0 Hz, 2H), 5.17 (d, *J* = 8.2 Hz, 1H), 4.52 (dd, *J* = 5.7, 7.6 Hz, 1H), 4.30 (dddd, *J* = 4.7, 6.3, 9.8, 11.5 Hz, 1H), 3.64 (td, *J* = 7.0, 11.7 Hz, 1H), 3.56 (td, *J* = 6.6, 11.7 Hz, 1H), 3.13 (dd, *J* = 4.7, 18.0 Hz, 1H), 2.93 (dd, *J* = 11.5, 18.0 Hz, 1H), 2.63 (dtd, *J* = 5.7, 6.4, 12.8 Hz, 1H), 2.50 (dqdd, *J* = 6.3, 6.9, 8.2, 12.5 Hz, 1H), 2.33 (td, *J* = 6.3, 12.5 Hz, 1H), 2.04 (tdd, *J* = 7.0, 7.6, 12.8 Hz, 1H), 1.85 (tdd, *J* = 6.4, 7.0, 12.9 Hz, 1H), 1.77 (dtd, *J* = 6.4, 7.0, 12.9 Hz, 1H), 1.53 (dt, *J* = 9.8, 12.5 Hz, 1H), 0.68 (d, *J* = 6.9 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 168.9, 167.3, 138.1, 128.3, 127.2, 127.0, 125.4, 57.2, 53.0, 48.0, 43.0, 40.6, 36.3, 28.2, 22.3, 14.9; HRMS (*m/z*): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_2$, 299.1760; found, 299.1758. IR (thin film): 1657, 1617, 1439, 747, 701 cm^{-1} .

(2*S*,3*R*,5*aR*,11*aR*)-2-Methyl-3-phenyloctahydro-5*H*-dipyrrolo[1,2-*a*:1',2'-*d*]

[1,4]diazepine-5,10(1*H*)-dione ((5*aR*,11*aR*)-3g**).**: Obtained as the major diastereomeric product (orange oil) from compound (*R*)-**10g** after deprotection (General Procedure D) to (*R*)-**1g** followed by cyclization using General Procedure F (61 mg, 59% yield, 87:21:1 d.r., ^1H NMR chemical shifts of minor diastereomers correlated with products (*5aS,11aS*)-**3g** and (*5aR,11aS*)-**3g**, respectively). The diastereomeric ratio was further enriched by repeated chromatography for 2D NMR characterization purposes. $[\alpha]^{23}_{\text{D}} +248$ (*c* 0.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.23 (m, 3H), 7.06 (d, *J* = 8.2 Hz, 2H), 5.10 (d, *J* = 7.8 Hz, 1H), 4.64 (ddd, *J* = 4.0, 8.0, 12.5 Hz, 1H), 4.61 (br dd, *J* = 6.6, 7.0 Hz, 1H), 3.67 (dd, *J* = 7.0, 12.0 Hz, 1H), 3.60 (dd, *J* = 6.6, 12.0 Hz, 1H), 2.85 (dd, *J* = 4.0, 18.5 Hz, 1H), 2.77 (br dd, *J* = 12.5, 18.5 Hz, 1H), 2.72 (dqdd, *J* = 6.3, 7.0, 7.8, 13.0 Hz, 2H), 2.58 (dddd, *J* = 6.3, 6.6, 7.0, 13.5 Hz, 1H), 2.12 (dt, *J* = 8.0, 13.0 Hz, 1H), 2.02 (br qd, *J* = 6.6, 13.5 Hz, 1H), 1.90 (tdd, *J* = 6.6, 7.0, 13.0 Hz, 1H), 1.80 (dtd, *J* = 6.3, 6.6, 13.0 Hz, 1H), 1.74 (dd, *J* = 6.3, 13.0 Hz, 1H), 0.66 (d, *J* = 7.0 Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 167.8, 167.1, 138.6, 128.3, 127.3, 126.6, 65.4, 57.8, 52.9, 48.4, 43.2, 37.3, 34.5, 28.3, 22.4, 14.8; HRMS (*m/z*): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_2$, 299.1760; found, 299.1761. IR (thin film): 1660, 1619, $750, 702\text{ cm}^{-1}$.

(2*S*,3*R*,5*aR*,11*aS*)-2-Methyl-3-phenyloctahydro-5*H*-dipyrrolo[1,2-*a*:1',2'-*d*]

[1,4]diazepine-5,10(1*H*)-dione ((5*aR*,11*aS*)-3g**).**: Obtained as the major diastereomeric product (orange oil) from compound (*R*)-**10g** after deprotection (General Procedure D) to (*R*)-**1g** followed by cyclization using General Procedure E (52 mg, 50% yield, 4:1:1 d.r., ^1H NMR chemical shifts of minor diastereomers correlated with products (*5aS,11aS*)-**3g** and (*5aR,11aR*)-**3g**). The diastereomeric ratio was further enriched by repeated chromatography for 2D NMR characterization purposes. $[\alpha]^{23}_{\text{D}} +27$ (*c* 0.4, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.37–7.28 (m, 2H), 7.27–7.21 (m, 1H), 7.14–7.08 (m, 2H), 5.06 (d, *J* = 9.0 Hz, 1H), 4.42 (t, *J* = 7.2 Hz, 1H), 4.06 (ddd, *J* = 5.1, 11.1, 11.3 Hz, 1H), 3.79 (td, *J* = 6.6, 12.0 Hz, 1H), 3.43 (td, *J* = 7.0, 12.0 Hz, 1H), 3.14 (dd, *J* = 11.1, 14.5 Hz, 1H), 2.88 (d, *J* = 14.5

Hz, 1H), 2.55 (d, $J = 14.1$ Hz, 1H), 2.44 (td, $J = 7.0, 13.7$ Hz, 1H), 2.21 (qd, $J = 6.6, 14.1$ Hz, 1H), 2.04 (td, $J = 5.3, 12.0$ Hz, 1H), 1.88–1.65 (m, 3H), 0.58 (d, $J = 6.6$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ (100 MHz, CDCl_3) δ 171.8, 166.4, 139.6, 128.2, 127.1, 126.4, 67.3, 61.6, 57.4, 47.6, 40.8, 39.6, 35.0, 30.9, 30.0, 22.9, 14.8; HRMS (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_2$, 299.1760; found, 299.1755. IR (thin film): 1639, 750, 702 cm^{-1} .

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(A) X-ray crystal structure of (S,S)-**3a**, with atomic displacement ellipsoids represented at the 50% contour probability level. (B) ϕ/ψ angles measured from the X-ray structure.

Figure 2.

Scope and products of DBU-mediated cyclization. Yields are reported over two steps (Boc deprotection, cyclization) from Boc-protected precursors **10**. Diastereomeric ratios are reported for purified products with reported isolated yields; in some cases crude NMR analysis indicated additional diastereomers had formed but were resolved chromatographically, see Experimental Section for details.

Figure 3.

Scope and products of the NaOMe-mediated cyclization. Yields are reported over two steps (Boc deprotection, cyclization) from Boc-protected precursors **10**. Diastereomeric ratios are reported for purified products.

Conditions screened:

Catalysts: Zr(Ot-Bu)₄/hydroxypyridine, Sn catalysts (Bu₂SnO, Otera's catalyst), anionic relay transfer (DBU with imidazole, pyrazole, benzotriazole, 1,2,4-triazole)

Solvents: CH₃CN in all cases except for Zr-catalyzed reactions (toluene)

Temperatures: 25 °C to 145 °C with both conventional & microwave heating.

Scheme 1.

Reaction screen targeting macrolactam **2** from amino acid-coupled homoallylic amines **1** produced pyrrolodiazepines **3** under basic conditions.

Scheme 2.

Reaction conditions producing (S,S)-3a.

5a $R^1 = Ph$

5b $R^1 = 3-BrPh$

5c $R^1 = cyclopropyl$

7 $R^1 = Ph$, 90% yield, 10:1 dr

8 $R^1 = 3-BrPh$, 73% yield, 17:1 dr

9 $R^1 = cyclopropyl$, 98% yield, 12:1 dr

Scheme 3.

Synthesis of enantioenriched homoallylic amines 7-9.

Scheme 4.

Conversion of homoallylic amines 7–9 to cyclization substrates 1a–g through Boc-protected intermediates 10a–g.

Scheme 5.
Mechanistic pathways for pyrrolodiazepinone formation.

Scheme 6.
Kinetic rationale for favored pyrrolidine cyclization.

Scheme 7. Divergent reaction and equilibrium pathways leading to (S,S)-3b or (R,R)-3b as the predominant thermodynamically-favored products for substrates (S)-1b and (R)-1b, respectively. Energies and energy differences are reported as relative Gibbs free energies in kcal/mol and were calculated with Jaguar (Schrodinger, Inc.) on DFT-optimized (B3LYP/6–31G**) structures in the absence of solvent.

Scheme 8. Divergent diastereoselectivities for major observed diastereomers of proline-derived substrates 1g.

Energy differences are reported as relative Gibbs free energies in kcal/mol and were calculated with Jaguar (Schrodinger, Inc.) on DFT-optimized (B3LYP/6-31G**) structures in the absence of solvent.

Table 1.

Yields of Boc-protected, enantioenriched homoallylic amine building blocks 10.

entry	starting material (R ¹)	AA (from Boc-AA-OH)	R ² (sidechain stereochemistry)	product 10	yield of 10
1	7 (Ph)	<i>L</i> -Phe	-CH ₂ Ph (<i>S</i>)	(<i>S</i>)- 10a	49%
2	7 (Ph)	<i>D</i> -Phe	-CH ₂ Ph (<i>R</i>)	(<i>R</i>)- 10a	54%
3	7 (Ph)	<i>L</i> -Leu	-CH ₂ ^{<i>i</i>} Pr (<i>S</i>)	(<i>S</i>)- 10b	52%
4	7 (Ph)	<i>D</i> -Leu	-CH ₂ ^{<i>i</i>} Pr (<i>R</i>)	(<i>R</i>)- 10b	63%
5	7 (Ph)	<i>L</i> -Val	- ^{<i>i</i>} Pr (<i>S</i>)	(<i>S</i>)- 10c	83%
6	7 (Ph)	<i>D</i> -Val	- ^{<i>i</i>} Pr (<i>R</i>)	(<i>R</i>)- 10c	67%
7	7 (Ph)	<i>L</i> -Ala	-CH ₃ (<i>S</i>)	(<i>S</i>)- 10d	69%
8	7 (Ph)	<i>D</i> -Ala	-CH ₃ (<i>R</i>)	(<i>R</i>)- 10d	75%
9	8 (3-BrPh)	<i>L</i> -Phe	-CH ₂ Ph (<i>S</i>)	(<i>S</i>)- 10e	91%
10	8 (3-BrPh)	<i>D</i> -Phe	-CH ₂ Ph (<i>R</i>)	(<i>R</i>)- 10e	75%
11	9 (CyPr)	<i>L</i> -Phe	-CH ₂ Ph (<i>S</i>)	(<i>S</i>)- 10f	95%
12	9 (CyPr)	<i>D</i> -Phe	-CH ₂ Ph (<i>R</i>)	(<i>R</i>)- 10f	66%
13	7 (Ph)	<i>L</i> -Pro	-CH ₂ CH ₂ CH ₂ - (<i>S</i>)	(<i>S</i>)- 10g	73%
14	7 (Ph)	<i>D</i> -Pro	-CH ₂ CH ₂ CH ₂ - (<i>S</i>)	(<i>R</i>)- 10g	67%

Table 2.

DFT-calculated (B3LYP/6–31G**) relative energies^a of pyrrolidine diastereomers arising from cyclization Pathway B from either *L*- or *D*-amino acid-derived substrates 1.

entry	starting material	relative energies for diastereomers of pyrrolidines 13 (kcal/mol) ^a			
		from <i>L</i> -AAs		from <i>D</i> -AAs	
		(<i>S</i> ,2 <i>S</i>)	(<i>S</i> ,2 <i>R</i>)	(<i>R</i> ,2 <i>R</i>)	(<i>R</i> ,2 <i>S</i>)
1	1a	+1.4	0	+1.0	0
2	1b	+0.1	0	+0.6	0
3	1c	0	+1.3	+1.7	0
4	1d	0	+0.02	0	+0.4

^(a) Energy differences are reported as the Gibbs free energy differences (in kcal/mol) for pyrrolidine diastereomeric pairs with similar amino acid-sidechain stereochemistry, and were calculated with Jaguar (Schrodinger, Inc.) on DFT-optimized structures in the absence of solvent.

Table 3.

Optimization of conditions intended to favor kinetic pyrrolidine intermediate (*S,S*)-11b gives rise to improved d.r. of final product (*S,S*)-3b at high percent conversion.

entry	equiv. DBU	temp (°C)	time (h)	% 3b	d.r.
1	1.0	145 ^a	0.75	100 ^c	11:3:1 ^f
2 ^b	1.0	60	48	87 ^d	6:1 ^e
3	5.0	25	18	53 ^c	22:1 ^f
4	5.0	100	1.5	91 ^c	17:1 ^f

(^a) Microwave heating;

(^b) CD₃CN solvent;

(^c) % conversion determined by UPLC-MS analysis;

(^d) % conversion determined by ¹H NMR;

(^e) determined by *in situ* ¹H NMR of reaction mixture;

(^f) determined by ¹H NMR of isolated product.

Table 4.Condition-dependent outcomes of pyrrolodiazepinone formation on *L*- and *D*-leucine substrates 10b.

entry	starting material	conditions	yield	3b ratio (S,S):(R,R)
1	<i>(R)</i> -10b	DBU/CH ₃ CN ^a	72%	3:1
2	<i>(R)</i> -10b	NaOMe/THF ^b	92%	1.4:1
3	<i>(R)</i> -10b	NaOMe/DMF ^c	94%	1:8
4	<i>(S)</i> -10b	DBU/CH ₃ CN ^a	72%	17:1
5	<i>(S)</i> -10b	NaOMe/DMF ^c	65%	4:1

^(a) Conditions: 5 equiv. DBU, CH₃CN (0.1M), 100 °C, 2 h;^(b) Conditions: 2 equiv. NaOMe, THF (0.1M), 25 °C, 1h;^(c) Conditions: 2 equiv. NaOMe, DMF (0.1M), 25 °C, 1 h

Table 5.

DFT-calculated (B3LYP-6-31g**) relative energies of pyrrolodiazepinone diastereomers arising from cyclization Pathway B from either *L*- or *D*-amino acid-derived substrates 1.

Entry	Starting Material	Relative energies ^a for diastereomers of pyrrolodiazepinones 3 (kcal/mol)			
		(5S,9aS)	(5S,9aR)	(5R,9aR)	(5R,9aS)
1	1a	+0.4	+1.8	0	+1.2
2	1b	+0.5	+2.3	0	+2.5
3	1c	+0.5	+1.3	0	+0.9
4	1d	+0.3	+2.0	0	+1.2

^aRelative energies are reported as Gibbs free energy differences in kcal/mol and were calculated with Jaguar (Schrodinger, Inc.) on DFT-optimized (B3LYP/6-31G**) structures in the absence of solvent.

Table 6.

Condition-dependent pyrrolodiazepinone-formation on *L*- and *D*-proline substrates 10g.

entry	starting material	conditions	yield	3g ratio (S,S):(R,R):(R,S):(S,R)
1	(<i>S</i>)-10g	A ^a	75%	14:1:0:0
2	(<i>S</i>)-10g	B ^b	61%	14:1:1:0
3	(<i>R</i>)-10g	A ^a	50%	1:1:4:0
4	(<i>R</i>)-10g	B ^b	59%	21:87:1:0

^(a) Condition A: 5 equiv. DBU, CH₃CN (0.1M), 100 °C, 2 h;^(b) Condition B: 2 equiv. NaOMe, DMF (0.1M), 25 °C, 1 h.