JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Extended Piperidine–Piperidinone Protein Interface Mimics

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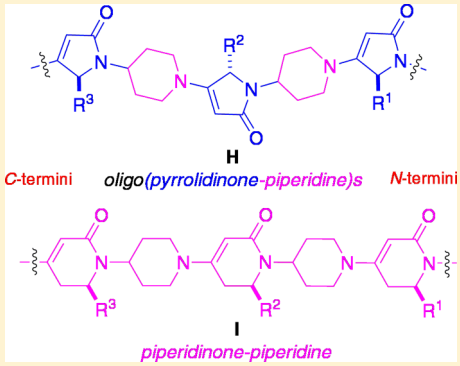
Supporting Information

ABSTRACT: Minimalist structures, **H** and **I**, were designed as protein interface mimics. Attributes of these chemotypes are (i) greater rigidity than conventional peptides, (ii) chiral and nonplanar heterocyclic backbones that are less prone to the hydrophobic aggregation effects, and (iii) potential to be prepared with a variety of side chains corresponding to natural amino acids. Intermediates, however, in the oligo(pyrrolidinone-piperidine)s **H** syntheses were vulnerable to epimerization. The origins of this epimerization were determined, then the study was focused on oligo(piperidinone–piperidine) compounds **I**. Mimics **I** were prepared via iterative couplings; a *penta*(piperidinone–piperidine) was prepared in this way. A series of lower homologues of this pentamer were crystallized and studied (single crystal X-ray), and four of them were used in a circular dichroism (CD) study. Thus, an estimate of 36 Å for the N-to-C distance of a typical conformation of the penta(piperidinone–piperidine) was made. CD spectra of four progressively longer oligomers allowed assignment of elipticity changes around 300 nm that can be attributed to increased conformational ordering of the longer oligomers in solution.



INTRODUCTION

Minimalist mimics of peptides and proteins are organic scaffolds that (i) access fewer conformations than peptides (are "semirigid") and (ii) display three or more amino acid side chains. Motivation for studies of minimalist mimics stems from their potential to perturb protein–protein interactions (PPIs). Noncovalent interaction energies at protein interfaces tend to be dominated by side chain to side chain interactions.[1] A minimalist mimic that presents side chains in orientations corresponding to one PPI component, called here the *protein–ligand*, has the potential to displace that ligand and bind to the other partner in the PPI, the *protein–receptor*.

Figure 1 shows illustrative minimalist mimics (**A**,[2] **B**,[3] **C**,[4] **D**,[5] **E**,[6] **F**[7]) reported since this area was reviewed in 2011.[8] For any particular PPI, a minimalist mimic scaffold has potential only if it is synthetically accessible with amino acid side chains corresponding to the protein–ligand at the interface region. The main shortcoming of designing generic secondary structure mimics is that secondary structures at PPI interfaces are usually distorted, and many interfaces do not involve secondary structures at all. This makes it difficult to decide where to overlay the mimic on the interface region and, therefore, which amino acids side chains should be incorporated.

If the appropriate region of overlay can be determined, the scaffold has to be made presenting those particular side chains. Mimic **A** has been formed from amino acids and is attractive in this regard. Sheet mimics **D**–**F** have so far been prepared only with methyl side chains, but there is potential to construct **D** and **E** from a variety of amino alcohols. Preparation of mimics **B**, **C**, and **F** with a variety of genetically encoded amino acid side chains would be more challenging.

In our view, the hidden potential of so-called minimalist mimics is they also populate conformations other than the targeted secondary structure.[8,9] We coined the term *universal mimics* to describe small molecules simultaneously populating conformations that resemble more than one secondary structure. This led us to appreciate that minimalist mimics in some situations can resemble regions of a PPI interface but not any particular secondary structure. This was enlightening because it forced us to realize that mimicry of secondary structures is not the real issue in designing small molecules to perturb PPIs.

In response, we conceived the Exploring Key Orientations (EKO) strategy. Briefly, in EKO, each set of three residues on a protein at a crystallographically characterized PPI interface is categorized in terms of six Cartesian coordinates corresponding to the three sets of Cα and Cβ atoms. Similarly, each kinetically and thermodynamically accessible conformation of a minimalist mimic of a PPI interface, an *interface mimic*, can be characterized in the same way, regardless of whether it resembles a secondary structure or not.

Papers from our laboratories have reported on the minimalist mimics **G**.[10] We were intrigued by the fact that small changes to the backbone structure **G** must affect the accessible conformations of these molecules and, therefore, the types of protein–ligand interface regions they can resemble.[11] However, if the compounds are not synthetically accessible, then it will be impossible to test their effects in a cellular environment. Our group has shown that mimics **G** can be prepared with a variety of amino acid side chains, but not without limitations.[10]

Received: February 9, 2015
Published: April 13, 2015

DOI: 10.1021/acs.joc.5b00300
J. Org. Chem. 2015, 80, 4450–4458

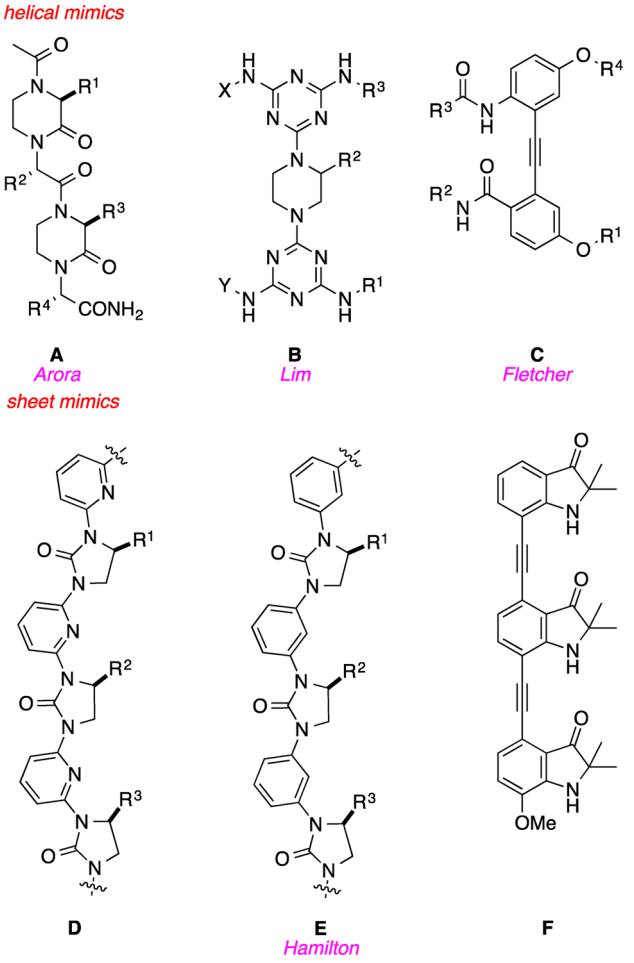


Figure 1. Recent examples of minimalist mimics.

Research described in this paper covers a brief investigation of the pyrrolinones–piperidine mimics **H** and more extensive work on the piperidinones–piperidines **I**,[11,12] particularly with respect to repeated application of the coupling chemistry used to prepare these molecules and some characteristics of the extended systems that are formed (Figure 2).

Scaffolds **G**–**I** have different conformational ensembles that orient the three side chains on each scaffold in different ways. Each scaffold will therefore overlay on different types of PPI interfaces, as determined using massive screening of the PDB with the data mining routine we developed as part of the EKO strategy. Illustrative data regarding what PPI interfaces EKO predicts will be impacted by scaffolds **H** and **I** are given in the Supporting Information (section E). This paper concerns attempts to make scaffold **H** and more successful syntheses of scaffolds **I** that are flexible with respect to the side chains that can be incorporated.

RESULTS AND DISCUSSION

Exploratory Studies On Pyrrolidinone–Piperidine Oligomers H. Synthesis of the chiral center pyrrolidines **G** necessitated S_N2 displacement of a triflate from an enantiomerically enriched, N-protected, 3-hydroxypyrrolidine; this was not a reaction that proceeded cleanly from starting material to product.[10] Superficially, syntheses of mimics **H** appeared to be more facile because reductive amination to give the diamines **1** does not introduce a chiral center. Diamines **1** were easy to prepare, and they were easily converted to piperidine-functionalized tetramic acid esters **2**.[13] The first chromatographic separation was required only at this stage; hence, these monomers were conveniently prepared in gram amounts (Scheme 1). Throughout this paper, compounds are numbered according to the scaffold with lower case one-letter codes

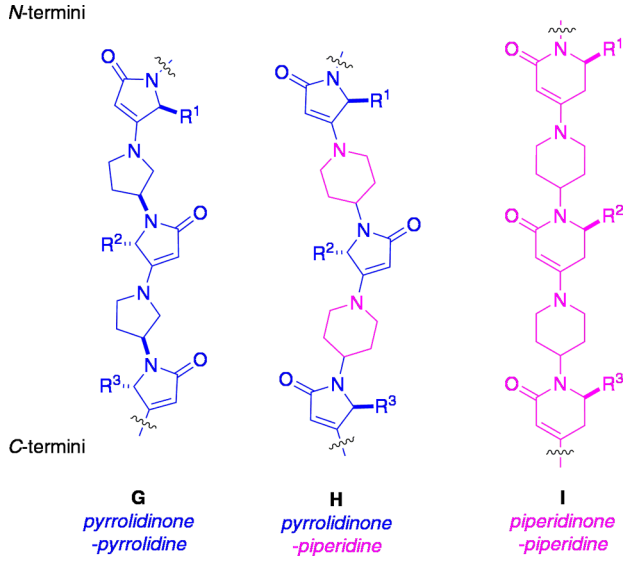
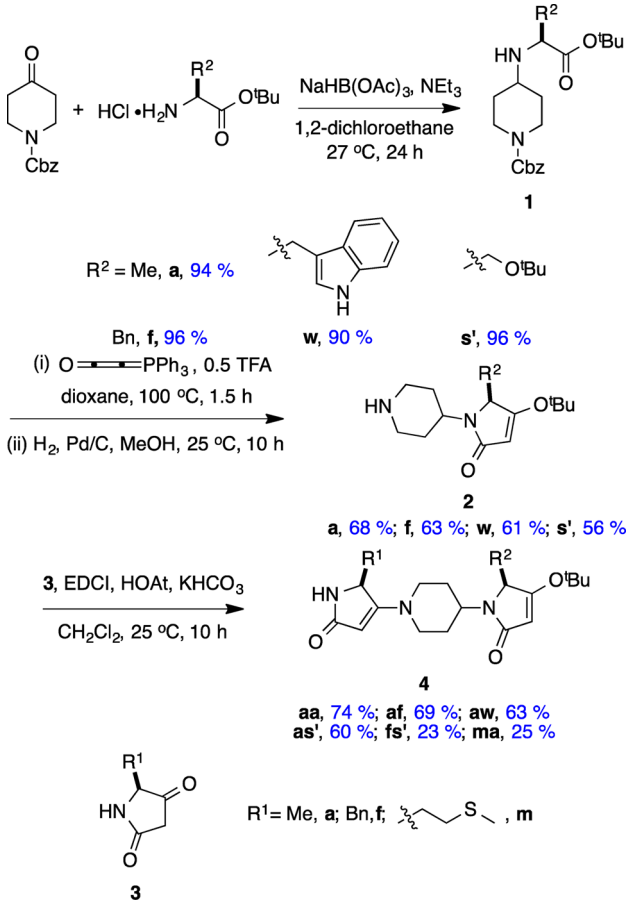


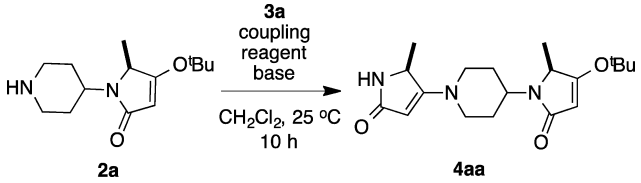
Figure 2. This paper focuses on minimalist mimics **H** and **I**, conceptually derived from **G**.

Scheme 1. Preparation of Pyrrolidine–Piperidines 4



DOI: 10.1021/acs.joc.5b00300
J. Org. Chem. 2015, 80, 4450–4458

Table 1. Optimization of Coupling the Piperidines 2a with the Tetramic Acids 3a



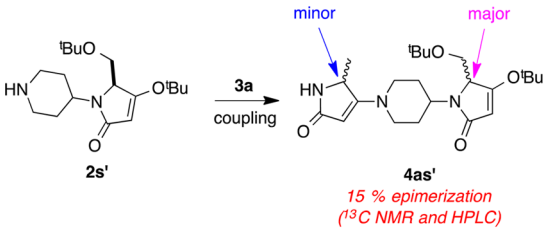
entry	activating reagent	base	additive	epimerization by ^{13}C NMR	isolated yield (%)
1	TBTU	TEA[a]		n.d.[c]	10
2	HBTU	TEA[a]		n.d.	23
3	PyBOP	TEA[a]		n.d.	complex mixture
4	TFFH	TEA[a]		n.d.	<10
5	EDCI	TEA[a]		n.d.	30
6	EDCI	TEA[a]	HOBt	n.d.	45
7	EDCI	TEA[a]	HOAt	n.d.	59
8	EDCI	KF[b]	HOAt	n.d.	40
9	EDCI	Li_2CO_3[b]	HOAt	n.d.	39
10	EDCI	Cs_2CO_3[b]	HOAt	10%	86
11	**EDCI**	**$KHCO_3$[b]**	**HOAt**	**none**	**74**
12	EDCI	$KHCO_3$[b]	oxyma[16]	n.d.	complex mixture
13	EDCI	$KHCO_3$[b]	*N*-hydroxysuccinimide	n.d.	10

[a]2.0 equiv of TEA. [b]5.0 equiv of the base. [c]Not determined.

relating their side chains to the parent amino acids (e.g., **f** for Phe, **s** for Ser, **s′** for the $-CH_2O^tBu$, **t** for $CH_2CH(OH)Me$, and **t′** for $CH_2CH(OBn)Me$; named from N- to C-terminus, just as in peptides).

Surprisingly, it proved to be difficult to couple the piperidines **2** with tetramic acids **3**, as compared with the pyrrolidines used in syntheses of scaffolds **G**. Considerable optimization of these reaction conditions was required, as documented in Table 1 and in a study of similar *β*-enamino ester syntheses from our lab.[14] The highlighted conditions (entry 11: EDCI, $KHCO_3$, HOAt[15]) afforded the scaffold with two side chains, **4aa**, more efficiently than any other set of conditions studied.

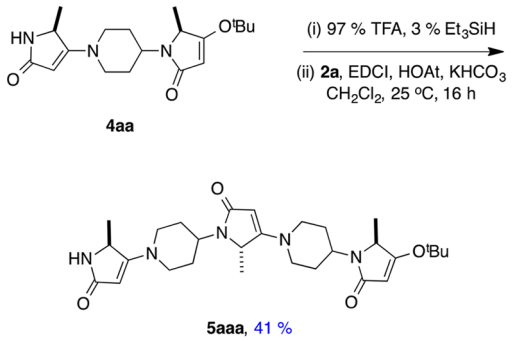
A major difficulty arose when the optimized conditions that gave **4aa** without epimerization were applied to make **4as′** and **4 fs′**; ∼15 and 30% epimerization was observed (by ^{13}C NMR and analytical HPLC), respectively (reaction 1). A series of



reaction 1

experiments were undertaken to determine which of the two chiral centers was most vulnerable to epimerization (SI, Figure S2). First, it was established that compound **2s′** is basic enough to mediate its own racemization when stored as a concentrated oil at room temperature overnight. Evidence for this assertion was from an experiment in which "aged" **2s′** was coupled with racemic tetramic acid **3a**, resulting in four stereoisomeric products that could be separated via analytical HPLC with a chiral support (Chiralpak AD). When freshly prepared **2s′** was coupled with optically pure tetramic acid **3a**, three products were observed: one of these was formed in even greater amounts when the experiment was repeated with aged (partially racemized) **2s′**. The fact that a significant amount of the fourth possible stereoisomer was not observed in the experiments involving optically pure **3a** indicates epimerization of the **2s′** fragment dominates. A possible reason for this is inductive stabilization of the enolate from **2s′** that would not affect **3a** or the N-terminal part of product **4as′**.

At this stage, it became clear that the targeted pyrrolidinone−piperidine oligomers **H** were too stereochemically delicate, especially if they contained side chains that somehow promoted epimerization. Consequently, we decided to focus our efforts on the piperidinone−piperidine systems **I** featured in the next section. Nevertheless, we were able to synthesize the three-side-chain system **5aaa** without epimerization (reaction 2).



reaction 2

Recently, we devised a strategy called Exploring Key Orientations on Secondary structures (EKOS). EKOS matches side chain orientations of a large number of accessible conformations of a minimalist mimic with sets of similar parameters in common secondary structures; this relates the conformations of the mimics in solution to the secondary structures they resemble most closely in terms of side chain

DOI: 10.1021/acs.joc.5b00300
J. Org. Chem. 2015, 80, 4450−4458

orientation.[9b] Application of the EKOS routine indicated accessible conformations of **5aaa** contain some that overlay on a sheet-turn-sheet motif more accurately than any of the conformers matched the other common secondary structures (3^{10}-, α-, π-helices; parallel and antiparallel β-sheets; and β-strands). Figure 3 shows the same overlay with conventional atom colors on the left and the ideal sheet-turn-sheet motif highlighted in purple on the right.

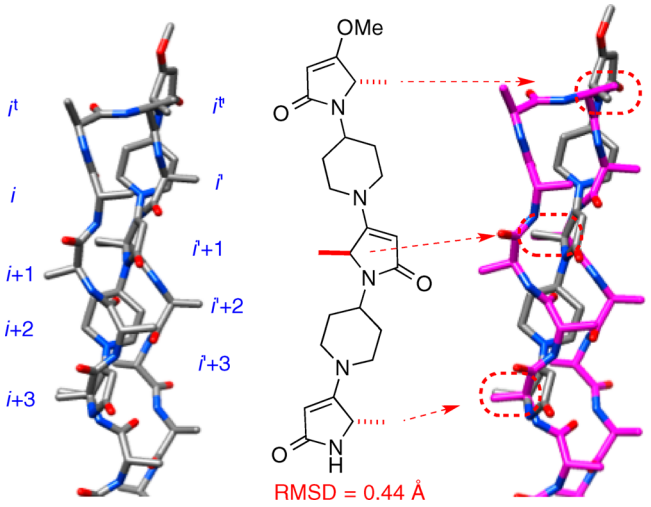


Figure 3. Overlay of **5aaa** on an ideal sheet-turn-sheet motif.

Piperidinone–Piperidine Oligomers I. Our laboratory has reported syntheses of compounds **6**,[11] and applied them to perturb PPIs involved in oligomerization of α-antithrombin.[12] The purpose of the current study was to see if the iterative coupling chemistry used to prepare compounds **6** could be applied to form extended systems and to elucidate some characteristics of the products formed (Figure 4).

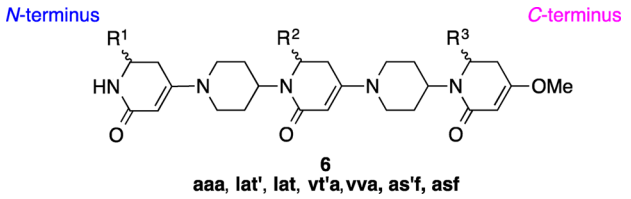
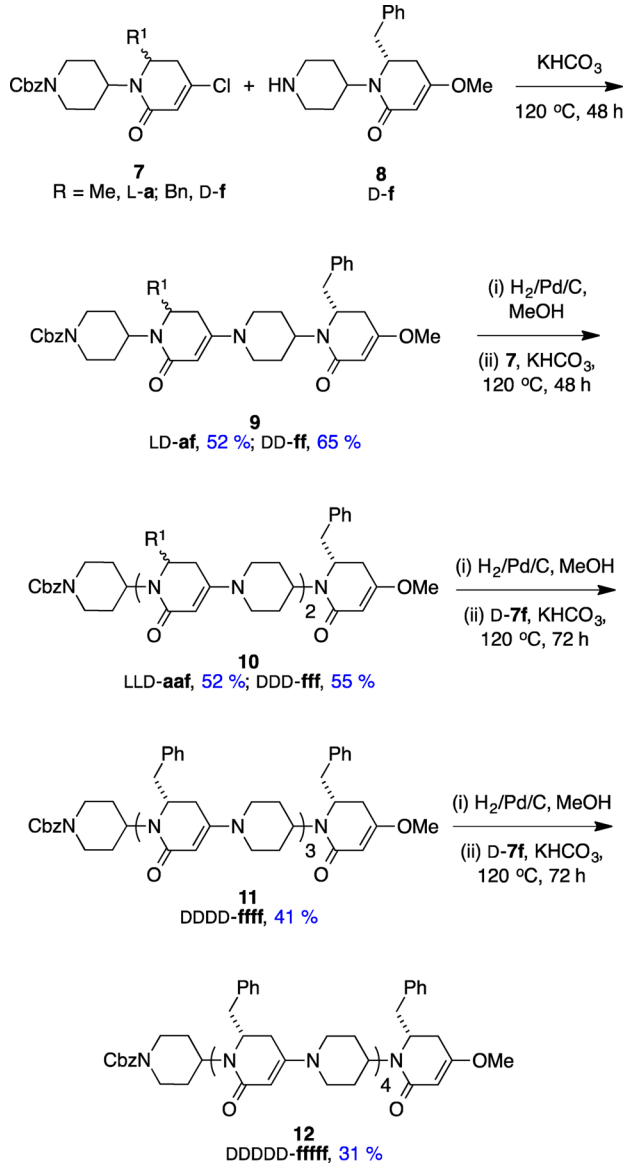


Figure 4. Scaffold **6** with various side chain functionalities.

Syntheses Of Extended Systems I. Compound 7 in Scheme 2 is analogous to an N-protected, C-activated amino acid. That Scheme illustrates how iterative couplings under elevated temperature and mildly basic conditions were suitable for synthesis of **12fffff** with five repeating units derived from Phe. Supporting Information Figure S1 shows the MALDI MS of this product has a single ion at the predicted m/z of 1507.8 for M + H (plus 1529.8 for M + Na, and 1545.8 for M + K). This product is considerably less polar than typical peptides, being soluble in dichloromethane, methanol, and DMSO.

Some Properties of the Extended Piperidinone–Piperidine Systems I. Three intermediates (**9af**, **13gg**, and **14-Bn′-faf**) were isolated[11] and crystallized in the course of the synthetic studies described above. Representations from X-ray crystal structures of those compounds are shown in Figure 5.

Scheme 2. Synthesis of the Piperidinones–Piperidine Mimic 12fffff with 10 Linked Rings



Solid state structures of **13gg**, **9af**, and **14-Bn′-faf** reveal that these molecules crystallize as conformers that have different dihedral angles for the linkages marked with red arrows in Figure 5. Rotation around bonds associated with these red arrows has a profound effect on the side chain orientations. This supports the assertion that minimalist mimics have the potential to adopt conformers that can overlay on more than one ideal secondary structure or interface region. Compounds **13gg**, **9af**, and **14-Bn′-faf** have 3, 4, and 5 piperidinone/piperidine rings, and they measure (N- to C-termini) 11.2, 15.1, and 17.5 Å, respectively. Those dimensions correspond to 3.73, 3.77, and 3.50 Å, respectively, per piperidinone or piperidine ring, and the difference between these figures (0.27 Å) reflects the extent of kinking or curvature in the overall conformation. None of these solid state conformations overlay very well on ideal secondary structures, but within this series, **13gg** and **9af** are the most extended (*cf* sheet structures), and **14-Bn′-faf** is most helical. Compound DDDDD-**12fffff** was not crystallized, but the solid state data suggests this compound might have N-

DOI: 10.1021/acs.joc.5b00300
J. Org. Chem. 2015, 80, 4450–4458

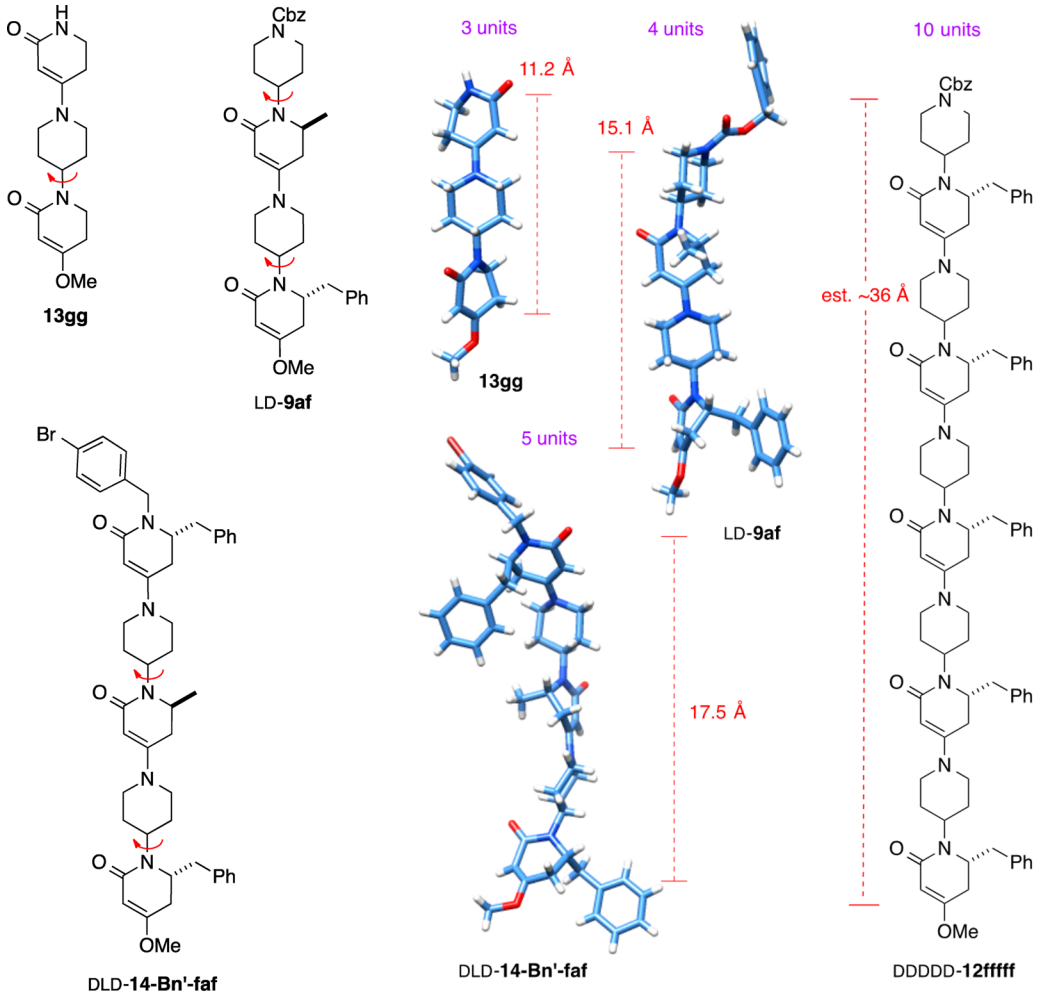


Figure 5. Scaffolds **13gg**, **9af**, and **14-Bn′-faf** were characterized via single crystal X-ray studies;[11] consequently, the N-to-C dimensions of **12fffff** were estimated to be around 36 Å.

to-C dimensions of (10 × 3.50) to (10 × 3.77), or around 36 Å in the solid state.

CD spectra of minimalist mimics are rarely informative because it is unusual to have a series that represents systematic changes to the scaffold structure.[17] However, in this particular study, several oligo(piperidinone−piperidine)s of different lengths were available, and this facilitated meaningful correlations of ellipticities with structure. Figure 6a shows UV spectra of compounds represented by the generic structure **J** (n = 1 is **9ff**; n = 2, **10fff**; n = 3, **11ffff**; and, n = 4, **12fffff**; D configuration throughout). Absorbance maxima at ∼290−310 nm (MeOH) are attributed to additive effects of the enamide chromophores (red box on **J**); more absorbance correlates with higher values of n. If the compounds were nonrandomly distributed among stereoisomeric secondary structures (e.g., right- and left-handed helices), then increased molar ellipticities would be expected as n increases. Figure 6b shows that molar ellipticities in the 290−310 nm wavelength region do, in fact, increase with n, implying some degree of ordering in solution.

CONCLUSION

This study has demonstrated mimics **I** are easier to prepare as a single stereoisomer than the closely related oligomers **H**. Solution phase syntheses of mono-, di-, tri-, tetra-, and pentaoligo(piperidinone−piperidine)s were convenient. Solid state structures of three compounds of intermediate lengths in this series showed they tend to adopt extended conformations and provided evidence to suggest a 36 Å longitudinal dimension for the pentamer **12fffff**. CD studies of milestone intermediates in this synthesis indicates the conformational ensemble tends toward progressively more ordered structures in solution.

EXPERIMENTAL SECTION

General Procedures. All reactions were carried out under nitrogen atmosphere with dry solvents under anhydrous conditions. Glassware was dried in an oven at 140 °C for a minimum of 6 h prior to use. Dry solvents were obtained by passing the previously degassed solvents through activated alumina columns. Reagents were purchased at a high commercial quality (typically 97% or higher) and used without further purification unless otherwise stated. Flash chromatography was performed using silica gel (230−600 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates with QF-254 indicator and visualized by UV or potassium permanganate stains. ^{1}H and ^{13}C spectra were recorded on a 300 or 400 MHz spectrometer and were calibrated using residual nondeuterated solvent as an internal reference. Chemical shifts (δ) are reported in parts per million, and coupling constants (J) are given in Hz. The following

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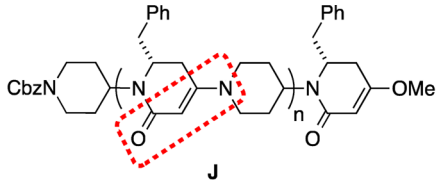
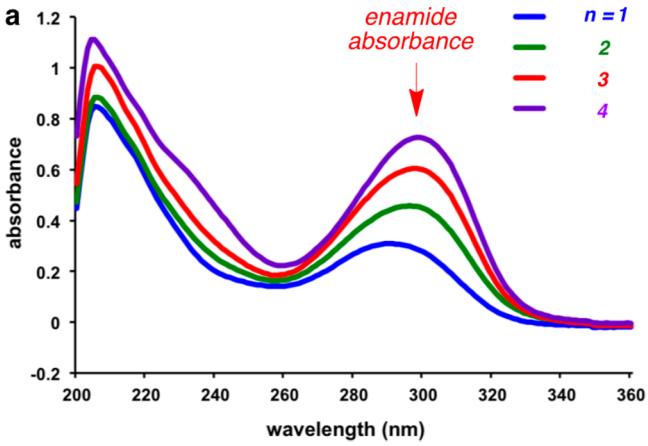


J



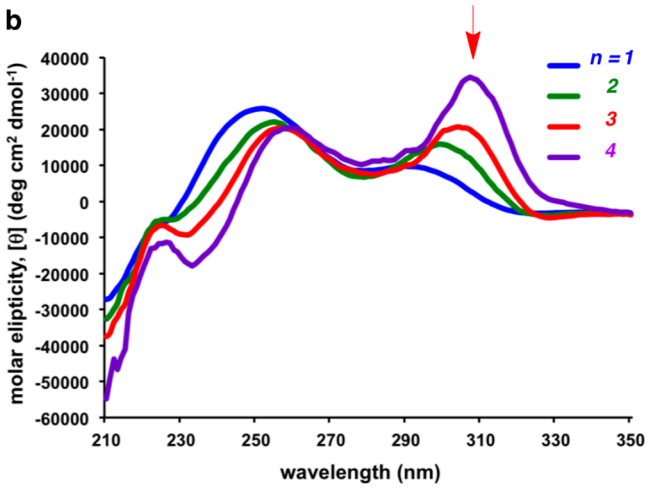


Figure 6. **a** UV; and, **b** CD spectra of **J** (n = 1 is **9ff**; n = 2, **10fff**; n = 3, **11ffff**; and, n = 4, **12fffff**) in MeOH. UV spectra were recorded at 20 μM, and CD at 200 μM.

abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dq = double quartet, m = multiplet, br = broad. HRMS were obtained using ESI or MALDI ionization. Melting points were recorded on an automated melting point apparatus and are uncorrected.

All the HPLC analyses were carried out with UV detection monitored at 254 nm. Analytical reversed phase HPLC analyses were performed with a 150 × 4.6 mm C-18 column using gradient conditions (10−90% acetonitrile in water, flow rate = 0.75 mL/min). Chiralpak AD (250 × 4.6 mm i.d.) column was utilized for the chiral HPLC analysis (hexanes: isopropyl alcohol 85:15, flow rate = 1 mL/min).

UV spectra were recorded on a UV spectrometer using a 10 mm quartz cuvette at 20 μM in MeOH. Circular dichroism spectra were recorded on a CD spectrometer using a 2 mm quartz cuvette at 200 μM in MeOH.

General Procedure for the Syntheses of 2. $NaBH(OAc)_3$ (6.36 g, 30.0 mmol) was added portionwise to a solution of L-alanine *tert*-butyl ester hydrochloride (1.82 g, 10.0 mmol), benzyl 4-oxopiperidine-1-carboxylate (2.33 g, 10.0 mmol), triethylamine (1.39 mL, 10.0 mmol) in 1,2-dichloroethane (70.0 mL) at 0 °C (ice bath) under nitrogen in a round-bottom flask. The ice bath was removed, and after stirring at 27 °C for 24 h, CH_2Cl_2 (100 mL) was added. The mixture was washed with saturated $NaHCO_3$ solution (3 × 100 mL) and then with brine (100 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give the reductive amination product 3.48 g (96% yield) as a colorless oil.

The product from the previous step (2.90 g, 8.0 mmol) was dissolved in dry dioxane (70.0 mL) in a round-bottom flask and heated to 100 °C under nitrogen atmosphere. Bestmann's ylide (recrystallized from PhMe, 5.32 g, 17.6 mmol, 2.2 equiv) was added in one portion, then 10 mL of TFA solution (0.4 M in dry dioxane) was added dropwise over 10 min. The reaction was monitored by ^{1}H NMR spectroscopy. After completion of the reaction (3 h), the solvent was removed under reduced pressure. The resulting oil was dissolved in dichloromethane and filtered through a thin layer of silica gel (∼1 cm). The silica gel was further washed with 9:1 dichloromethane/ethyl acetate. The solvent was removed under reduced pressure to give the cyclized product contaminated with Ph_3PO.

Pd/C (10 wt %; 0.85 g, 0.10 equiv Pd) was carefully added to a stirred solution of the crude cyclization product in methanol (60 mL) under nitrogen at 25 °C. The reaction was evacuated, refilled with N_2, and placed under an atmosphere of H_2 (1 atm, balloon) for 10 h. The reaction mixture was purged with N_2 and filtered over a pad of Celite under a gentle vacuum (*SAFETY NOTE*: Do not let the pad run dry). The Celite pad was washed with methanol (2 × 15 mL), and the combined filtrates were concentrated. The residue was purified by flash chromatography (SiO_2, 3−5% $MeOH/CH_2Cl_2$ containing 1% Et_3N) to afford the product **2a** (1.37 g, 68%) as a white solid.

*(S)-4-(tert-Butoxy)-5-methyl-1-(piperidin-4-yl)-1H-pyrrol-2(5H)-one (**2a**).* White solid, 1.37 g, 68% yield over two steps; mp = 130.5−131.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 (1H, s), 4.01−3.81 (2H, m), 3.18−3.04 (2H, m), 2.71−2.56 (3H, m), 1.83−1.61 (4H, m), 1.39 (9H, s), 1.29 (3H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 171.8, 95.2, 81.4, 56.6, 49.6, 46.3, 46.2, 32.9, 31.0, 27.4, 18.7. HRMS (ESI-TOF): m/z calcd for $C_{14}H_{24}N_2O_2$ $[M + H]^+$ 253.1916; found 253.1908.

*(S)-5-Benzyl-4-(tert-butoxy)-1-(piperidin-4-yl)-1H-pyrrol-2(5H)-one (**2f**).* White solid, 0.83 g from L-phenylalanine *tert*-butyl ester hydrochloride (1.03 g, 4.00 mmol), 63% yield over three steps; mp = 218.8−219.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25−7.13 (5H, m), 5.30−5.22 (1H, br), 4.92 (1H, s), 4.16 (1H, t, J = 5.1 Hz), 3.64−3.52 (1H, m), 3.28−3.18 (2H, m), 3.09 (1H, dd, J = 5.1, 14.4 Hz), 3.00 (1H, dd, J = 5.1, 14.4 Hz), 2.78−2.59 (2H, m), 2.35−2.04 (2H, m), 1.89−1.69 (2H, m), 1.28 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 170.6, 136.0, 129.4, 128.1, 126.7, 96.8, 82.0, 61.6, 50.7, 45.6, 45.5, 36.9, 30.1, 29.7, 27.3. HRMS (ESI-TOF): m/z calcd for $C_{20}H_{28}N_2O_2$ $[M + H]^+$ 329.2229; found 329.2220.

*(S)-5-((1H-Indol-3-yl)methyl)-4-(tert-butoxy)-1-(piperidin-4-yl)-1H-pyrrol-2(5H)-one (**2w**).* White solid, 1.12 g from L-tryptophan *tert*-butyl ester hydrochloride (1.48 g, 5.00 mmol), 61% yield over three steps; mp = 197.9−198.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (1H, br), 7.58 (1H, d, J = 6.6 Hz),

DOI: 10.1021/acs.joc.5b00300
J. Org. Chem. 2015, 80, 4450−4458

7.32 (1H, d, J = 6.6 Hz), 7.16−7.03 (3H, m), 4.83 (1H, s), 4.29 (1H, t, J = 4.2 Hz), 3.38−3.19 (2H, m), 3.19−3.04 (2H, m), 2.66−2.53 (2H, m), 2.53−2.32 (1H, br), 2.05−1.69 (4H, m), 1.07 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 170.7, 135.5, 128.1, 122.2, 121.6, 118.8, 118.6, 111.1, 108.7, 96.6, 81.6, 60.7, 50.9, 46.4, 46.3, 32.3, 31.4, 26.8, 25.4. HRMS (ESI-TOF): m/z calcd for $C_{22}H_{29}N_3O_2$ $[M + H]^+$ 368.2338; found 368.2324.

*(S)-4-(tert-Butoxy)-5-(tert-butoxymethyl)-1-(piperidin-4-yl)-1H-pyrrol-2(5H)-one (**2s′**).* Colorless oil, 0.91 g from *O-tert*-butyl-L-serine *tert*-butyl ester hydrochloride (1.27 g, 5.00 mmol), 56% yield over three steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 (1H, s), 3.97−3.82 (2H, m), 3.67 (1H, dd, J = 2.4, 9.3 Hz), 3.39 (1H, dd, J = 5.1, 9.3 Hz), 3.18−3.03 (2H, m), 2.64−2.51 (3H, m), 2.08−1.82 (2H, m), 1.79−1.58 (2H, m), 1.38 (9H, s), 1.11 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 168.2, 96.9, 81.4, 72.9, 62.0, 61.2, 50.5, 46.6, 46.4, 32.1, 31.2, 27.4, 27.3. HRMS (ESI-TOF): m/z calcd for $C_{18}H_{32}N_2O_3$ $[M + H]^+$ 325.2491; found 325.2479.

General Procedure for the Syntheses of 4. To a stirred solution of **2a** (126.2 mg, 0.5 mmol), **3a** (113.1 mg, 1.0 mmol), and HOAt (149.7 mg, 1.1 mmol) in dry dichloromethane (5 mL) under nitrogen in a round-bottom flask, $KHCO_3$ (0.25 g, 2.5 mmol) and EDCI (210.9 mg, 1.1 mmol) were added, and the resulting yellow mixture was stirred at room temperature for 10 h. After the reaction was complete, dichloromethane (10 mL) was added to precipitate the urea byproduct. The solvent was decanted, and the dark red solid was washed twice with dichloromethane (2 × 10 mL). The organic solution was combined and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 3−5% MeOH/CH_2Cl_2) to afford the product **4** (128.4 mg, 74% yield) as a colorless oil.

*(S)-4-(tert-Butoxy)-5-methyl-1-(1-((S)-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-3-yl)piperidin-4-yl)-1H-pyrrol-2(5H)-one (**4aa**).* Colorless oil, 128.4 mg, 74% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (1H, s), 4.95 (1H, s), 4.66 (1H, s), 4.16 (1H, q, J = 6.3 Hz), 4.09−3.95 (1H, m), 3.83 (1H, q, J = 6.6 Hz), 3.59−3.40 (2H, m), 3.00−2.83 (2H, m), 1.99−1.66 (4H, m), 1.38 (9H, s), 1.33 (3H, d, J = 6.3 Hz), 1.28 (3H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 172.3, 171.9, 169.4, 95.1, 90.8, 81.6, 56.7, 52.3, 49.2, 48.0, 47.8, 31.2, 28.9, 27.4, 20.5, 18.7. HRMS (ESI-TOF): m/z calcd for $C_{19}H_{29}N_3O_3$ $[M + H]^+$ 348.2287; found 348.2284.

*(S)-5-Benzyl-4-(tert-butoxy)-1-(1-((S)-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-3-yl)piperidin-4-yl)-1H-pyrrol-2(5H)-one (**4af**).* Colorless oil, 145.9 mg from **2f** (164.0 mg, 0.5 mmol) and **3a** (113.1 mg, 1.0 mmol), 69% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.09 (5H, m), 6.17 (1H, s), 4.88 (1H, s), 4.65 (1H, s), 4.16−4.08 (2H, m), 3.62−3.38 (3H, m), 3.11 (1H, dd, J = 4.8, 14.7 Hz), 2.92 (1H, dd, J = 5.4, 14.7 Hz), 2.85−2.70 (2H, m), 2.20−2.14 (1H, m), 2.02−1.96 (1H, m), 1.83−1.79 (1H, m), 1.72−1.67 (1H, m), 1.38−1.26 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 173.7, 170.3, 169.4, 136.2, 129.2, 128.2, 126.9, 96.8, 90.8, 81.9, 61.7, 52.2, 51.1, 48.1, 47.8, 37.3, 29.8, 29.1, 27.3, 20.5. HRMS (ESI-TOF): m/z calcd for $C_{25}H_{33}N_3O_3$ $[M + H]^+$ 424.2600; found 424.2605.

*(S)-5-((1H-Indol-3-yl)methyl)-4-(tert-butoxy)-1-(1-((S)-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-3-yl)piperidin-4-yl)-1H-pyrrol-2(5H)-one (**4aw**).* Light yellow oil, 145.5 mg from **2w** (183.5 mg, 0.5 mmol) and **3a** (113.1 mg, 1.0 mmol), 63% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (1H, s), 7.53 (1H, d, J = 7.8 Hz), 7.34 (1H, d, J = 7.5 Hz), 7.16−7.04 (2H, m), 7.01 (1H, d, J = 2.1 Hz), 6.19 (1H, s), 4.91 (1H, s), 4.60 (1H, s), 4.26 (1H, t, J = 5.1 Hz), 4.00 (1H, q, J = 6.3 Hz), 3.89−3.77 (1H, m), 3.44−3.06 (4H, m), 2.83−2.64 (2H, m), 2.12−1.54 (4H, m), 1.28 (3H, d, J = 6.3 Hz), 1.23 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 173.8, 170.9, 169.5, 135.8, 127.7, 122.2, 121.8, 119.0, 118.4, 111.4, 109.3, 96.4, 90.4, 81.9, 61.3, 52.2, 50.4, 48.1, 47.8, 30.3, 28.7, 27.1, 26.6, 20.4. HRMS (ESI-TOF): m/z calcd for $C_{27}H_{34}N_4O_3$ $[M + H]^+$ 463.2709; found 463.2692.

*(S)-4-(tert-Butoxy)-5-(tert-butoxymethyl)-1-(1-((S)-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-3-yl)piperidin-4-yl)-1H-pyrrol-2(5H)-one (**4as′**).* Colorless oil, 100.4 mg from **2s′** (130.0 mg, 0.4 mmol) and **3a** (90.5 mg, 0.8 mmol), 60% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (1H, s), 4.99 (1H, s), 4.66 (1H, s), 4.15 (1H, q, J = 6.6 Hz), 4.10−3.95 (1H, m), 3.92 (1H, dd, J = 2.1, 6.6 Hz), 3.66 (1H, dd, J = 2.4, 9.6 Hz), 3.59−3.39 (2H, m), 3.28 (1H, dd, J = 6.9, 9.6 Hz), 3.00−2.81 (2H, m), 2.34−2.00 (2H, m), 1.82−1.59 (2H, m), 1.41 (9H, s), 1.34 (3H, d, J = 6.6 Hz), 1.14 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 172.8, 169.6, 168.1, 96.7, 90.2, 81.8, 73.4, 62.7, 62.3, 52.3, 49.9, 48.2, 47.9, 30.2, 28.7, 27.5, 27.4, 20.5. HRMS (ESI-TOF): m/z calcd for $C_{23}H_{37}N_3O_4$ $[M + H]^+$ 420.2862; found 420.2878.

*(S)-1-(1-((S)-2-Benzyl-5-oxo-2,5-dihydro-1H-pyrrol-3-yl)-piperidin-4-yl)-4-(tert-butoxy)-5-(tert-butoxymethyl)-1H-pyrrol-2(5H)-one (**4 fs′**).* Colorless oil, 45.5 mg from **2s′** (130.0 mg, 0.4 mmol) and **3f** (151.4 mg, 0.8 mmol), 23% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.18 (5H, m), 5.22 (1H, s), 5.01 (1H, s), 4.73 (1H, d, J = 2.4 Hz), 4.28 (1H, dd, J = 4.5, 9.9 Hz), 4.13−3.99 (1H, m), 3.95 (1H, dd, J = 2.4, 6.9 Hz), 3.73−3.46 (3H, m), 3.34−3.27 (1H, m), 3.16 (1H, dd, J = 2.7, 7.8 Hz), 3.09−2.89 (2H, m), 2.55 (1H, dd, J = 9.6, 13.8 Hz), 2.21−2.09 (2H, m), 1.88−1.67 (2H, m), 1.42 (9H, s), 1.14 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 172.8, 168.1, 167.6, 137.1, 129.0, 128.8, 127.1, 96.8, 91.9, 81.8, 73.4, 62.8, 62.4, 57.7, 50.0, 48.5, 48.1, 41.3, 30.2, 28.7, 27.5, 27.4. HRMS (ESI-TOF): m/z calcd for $C_{29}H_{41}N_3O_4$ $[M + H]^+$ 496.3176; found 496.3163.

*(S)-4-(tert-Butoxy)-5-methyl-1-(1-((S)-2-(2-(methylthio)-ethyl)-5-oxo-2,5-dihydro-1H-pyrrol-3-yl)piperidin-4-yl)-1H-pyrrol-2(5H)-one (**4ma**).* Light yellow oil, 50.9 mg from **2a** (126.2 mg, 0.5 mmol) and **3m** (173.2 mg, 1.0 mmol), 25% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (1H, s), 5.00 (1H, s), 4.78 (1H, d, J = 1.5 Hz), 4.33−4.29 (1H, m), 4.11−3.98 (1H, m), 3.87 (1H, q, J = 6.6 Hz), 3.60−3.42 (2H, m), 3.04−2.91 (2H, m), 2.60 (2H, t, J = 7.8 Hz), 2.12 (3H, s), 2.10−1.71 (6H, m), 1.44 (9H, s), 1.32 (3H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 172.4, 171.9, 167.7, 95.2, 92.4, 81.7, 56.7, 55.6, 49.2, 48.3, 48.1, 33.8, 31.2, 30.4, 28.9, 27.4, 18.7, 15.7. HRMS (ESI-TOF): m/z calcd for $C_{21}H_{33}N_3O_3S$ $[M + H]^+$ 408.2321; found 408.2314.

Procedure for the Syntheses of 5aaa. Compound **4aa** (277.7 mg, 0.5 mmol) was treated with TFA/Et_3SiH (97:3, 2.5 mL) at 25 °C. The reaction was stirred in a vented capped flask until complete disappearance of starting material (monitored by NMR spectroscopy, ∼ 1 h). Toluene (10 mL) was added, and the reaction mixture was concentrated in vacuo. Toluene (2 × 10 mL) was used to azeotrope residual TFA. The crude oil was dissolved in dichloromethane (4 mL) and filtered through a thin layer of silica gel (∼0.5 cm) to remove some polar impurities. The silica gel was washed with 5% MeOH/CH_2Cl_2 five times (5 × 5 mL). The organic fractions were combined, and the solvent was removed in vacuo to give the deprotected

DOI: 10.1021/acs.joc.5b00300
J. Org. Chem. 2015, 80, 4450−4458

4aa as a white solid. The white solid was dried under high vacuum and used directly in the next step without further purification.

To a stirred solution of **2a** (75.6 mg, 0.3 mmol), deprotected **4aa** from previous step, and HOAt (89.8 mg, 0.66 mmol) in dry dichloromethane (2 mL) under nitrogen, $KHCO_3$ (150 mg, 1.5 mmol) and EDCI (126.5 mg, 0.66 mmol) were added, and the resulting yellow mixture was stirred at room temperature for 16 h. After the reaction was complete, dichloromethane (4 mL) was added to precipitate the urea byproduct. The solvent was decanted, and the light red solid was washed twice with dichloromethane (2 × 3 mL). The organic solution was combined and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 4−6% MeOH/CH_2Cl_2) to afford the product **5aaa**.

*(S)-4-(tert-Butoxy)-5-methyl-1-(1-((S)-2-methyl-1-(1-((S)-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-3-yl)piperidin-4-yl)-5-oxo-2,5-dihydro-1H-pyrrol-3-yl)piperidin-4-yl)-1H-pyrrol-2(5H)-one (**5aaa**).* Colorless oil, 64.6 mg, 41% yield over two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (1H, s), 4.97 (1H, s), 4.77 (1H, s), 4.71 (1H, d, J = 1.8 Hz), 4.18 (1H, q, J = 6.3 Hz), 4.12−3.91 (3H, m), 3.86 (1H, q, J = 6.3 Hz), 3.59−3.33 (4H, m), 3.06−2.84 (4H, m), 2.19−1.68 (8H, m), 1.42 (9H, s), 1.35 (6H, d, J = 6.3 Hz), 1.30 (3H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 172.8, 172.4, 171.9, 169.3, 167.6, 95.2, 92.3, 90.8, 81.7, 56.8, 54.3, 52.1, 49.6, 49.3, 48.3, 48.1, 48.0, 47.9, 31.3, 31.0, 29.0, 28.7, 27.4, 21.1, 20.6, 18.6. HRMS (MALDI-TOF): m/z calcd for $C_{29}H_{43}N_5O_4$ $[M + H]^+$ 526.3388; found 526.3384.

General Procedure A for Coupling Reaction. Anhydrous $KHCO_3$ powder (4.00 g, 40.0 mmol, 40.0 equiv) was added to a 0.5 M solution of D-**8f** (300.5 mg, 1.0 mmol, 1.0 equiv) in CH_2Cl_2. The vinyl chloride D-**7f** (439.0 mg, 1.0 mmol, 1.0 equiv) was then added as a 0.5 M solution in CH_2Cl_2 to the reaction mixture. While stirring at room temperature, the solvent was removed with nitrogen. The resulting solid was heated to 120 °C under N_2. After 24 h, 2 mL of anhydrous 1,4-dioxane was added, stirred for 10 min and then removed with nitrogen. The mixture was kept at 120 °C under N_2 for another 24 h. After the reaction finished, the mixture was cooled to room temperature. CH_2Cl_2 (20 mL) was added, and the inorganic solids were removed by filtration. The solution was concentrated to give the crude product. The product was purified by flash chromatography (SiO_2, 3−5% MeOH/CH_2Cl_2) to afford the product DD-**9ff**.

General Procedure B For Cbz Deprotection. Pd/C (10 wt %; 53 mg, 0.10 equiv Pd) was carefully added to a stirred solution of DD-**9ff** (351 mg, 0.5 mmol) in 5 mL methanol (0.1 M) under nitrogen at 25 °C. The reaction was placed under an atmosphere of hydrogen (1 atm, balloon) for 12 h. After 12 h, the flask was purged with N_2. The reaction mixture was filtered over a Celite pad and concentrated to afford the Cbz deprotected product. The product was used in the next step without further purification.

*Benzyl 4-((R)-2-benzyl-4-(4-((R)-2-benzyl-4-methoxy-6-oxo-3,6-dihydropyridin-1(2H)-yl)piperidin-1-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl)piperidine-1-carboxylate (DD-**9ff**).* White foamy solid, 454.3 mg from coupling of D-**7f** and D-**8f** with general procedure A, 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 12H), 7.18−7.04 (m, 3H), 5.16 (s, 3H), 5.06 (s, 1H), 4.77−4.61 (m, 1H), 4.59−4.50 (m, 1H), 4.33 (br, 2H), 3.75−3.60 (m, 7H), 3.14−2.71 (m, 8H), 2.54 (dd, J = 16.9, 5.6 Hz, 1H), 2.34−2.09 (m, 3H), 1.99−1.55 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 166.2, 165.7, 155.2, 153.7, 138.4, 137.7, 136.8, 129.3, 129.2, 128.8, 128.7, 128.5, 128.0, 127.9, 126.9, 126.8, 94.6, 93.1, 67.2, 55.7, 52.2, 51.6, 51.5, 50.4, 46.0, 45.7, 43.9, 43.8, 39.5, 39.2, 31.1, 30.8, 30.1, 29.8, 29.7, 28.6; HRMS (ESI-TOF): m/z calcd for $C_{43}H_{50}N_4O_5$ $[M + H]^+$ 703.3859; found 703.3849.

Benzyl 4-((*R*)-2-benzyl-4-(4-((*R*)-2-benzyl-4-(4-((*R*)-2-benzyl-4-methoxy-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)piperidin-1-yl)-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)piperidin-1-yl)-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)piperidine-1-carboxylate (DDD-**10fff**). DD-**9ff** (351.3 mg, 0.5 mmol) was deprotected with general procedure B, and the product was coupled with D-**7f** (220.5 mg, 0.5 mmol) using general procedure A to give DDD-**10fff** as a light yellow oil. 268.8 mg, 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.05 (m, 20H), 5.18 (s, 3H), 5.05 (s, 1H), 5.06 (s, 1H), 4.76−4.48 (m, 3H), 4.35 (br, 2H), 3.74−3.63 (m, 10H), 3.12−2.76 (m, 12H), 2.55 (dd, J = 16.8, 5.6 Hz, 1H), 2.33−2.13 (m, 5H), 2.00−1.61 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 166.2, 165.7, 155.2, 153.7, 153.6, 138.4, 138.3, 137.7, 136.8, 129.3, 129.2, 128.8, 128.7, 128.7, 128.5, 128.0, 127.9, 126.9, 126.9, 126.8, 94.6, 93.1, 92.9, 67.2, 55.7, 52.2, 52.0, 51.6, 51.5, 50.9, 50.4, 46.0, 45.7, 45.7, 43.9, 43.8, 39.5, 39.2, 39.1, 31.1, 30.8, 30.2, 30.1, 29.8, 29.6, 28.8, 28.5; HRMS (ESI-TOF): m/z calcd for $C_{60}H_{70}N_6O_6$ $[M + H]^+$ 971.5435; found 971.5437.

Benzyl 4-((*R*)-2-benzyl-4-(4-((*R*)-2-benzyl-4-(4-((*R*)-2-benzyl-4-(4-((*R*)-2-benzyl-4-methoxy-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)piperidin-1-yl)-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)-piperidin-1-yl)-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)piperidin-1-yl)-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)piperidine-1-carboxylate (DDDD-**11ffff**). DDD-**10fff** (194.9 mg, 0.2 mmol) was deprotected with general procedure B, and the product was coupled with D-**7f** (175.6 mg, 0.4 mmol) using general procedure A to give DDDD-**11ffff** as a light yellow oil. 99.6 mg, 41% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.08 (m, 25H), 5.19 (s, 3H), 5.10−5.02 (m, 3H), 4.79−4.47 (m, 4H), 4.35 (br, 2H), 3.80−3.61 (m, 13H), 3.14−2.76 (m, 16H), 2.55 (dd, J = 16.8, 5.8 Hz, 1H), 2.39−2.16 (m, 7H), 2.03−1.57 (m, 16H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 166.3, 166.2, 165.7, 155.2, 153.7, 153.6, 138.4, 138.3, 138.3, 137.7, 136.8, 129.2, 129.2, 128.8, 128.7, 128.7, 128.5, 128.0, 127.9, 126.9, 126.9, 126.8, 94.6, 93.1, 92.9, 92.9, 67.2, 55.7, 52.2, 52.0, 51.7, 51.6, 50.9, 50.9, 50.3, 46.0, 46.0, 45.8, 45.7, 43.9, 43.8, 39.5, 39.2, 39.2, 31.0, 30.8, 30.2, 30.1, 29.9, 29.8, 29.7, 28.8, 28.6; HRMS (MALDI-TOF): m/z calcd for $C_{77}H_{90}N_8O_7$ $[M + Na]^+$ 1261.6824; found 1261.6881.

Benzyl 4-((*R*)-2-benzyl-4-(4-((*R*)-2-benzyl-4-(4-((*R*)-2-benzyl-4-(4-((*R*)-2-benzyl-4-(4-((*R*)-2-benzyl-4-methoxy-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)piperidin-1-yl)-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)piperidin-1-yl)-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)piperidin-1-yl)-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)-piperidin-1-yl)-6-oxo-3,6-dihydropyridin-1(2*H*)-yl)piperidine-1-carboxylate (DDDDD-**12fffff**): DDDD-**11ffff** (75.1 mg, 0.06 mmol) was deprotected with general procedure B, and the product was coupled with D-**7f** (88.5 mg, 0.2 mmol) using general procedure A to give DDDDD-**12fffff** as a light yellow oil. 27.6 mg, 31% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.07 (m, 30H), 5.21−5.17 (m, 3H), 5.10−5.02 (m, 4H), 4.77−4.49 (m, 5H), 4.35 (br, 2H), 3.77−3.62 (m, 16H), 3.15−2.79 (m, 20 H), 2.56 (dd, J = 16.9, 5.6 Hz, 1H), 2.37−2.15 (m, 9H), 2.09−1.61 (m, 20H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 166.3, 166.2, 165.7, 155.2, 153.7, 153.6, 138.4, 138.3, 138.3, 137.7, 136.8, 129.3, 129.2, 128.8, 128.7, 128.7, 128.5, 128.0,

DOI: 10.1021/acs.joc.5b00300
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127.9, 126.9, 126.9, 126.8, 94.6, 93.1, 92.9, 67.2, 55.7, 52.2, 52.0, 51.7, 51.5, 51.0, 50.9, 50.4, 46.0, 45.8, 45.7, 43.9, 43.8, 39.5, 39.2, 39.2, 31.0, 30.2, 30.1, 29.8, 29.7, 28.8, 28.5; HRMS (MALDI-TOF): m/z calcd for $C_{94}H_{110}N_{10}O_8$ $[M + Na]^+$ 1529.8398; found 1529.8406.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all new compounds. Procedures for quenched molecular dynamics and EKOS analysis. Detailed procedure and analysis for epimerization study in the synthesis of **4as**′ with NMR and HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

■ ACKNOWLEDGMENTS

Financial support for this project was provided by the National Institutes of Health (GM087981), and the Robert A. Welch Foundation (A-1121) and the High Impact Research (HIR (UM.C/625/1/HIR/MOHE/MED/17 and UM.C/625/1/HIR/MOHE/MED/33) from the Ministry of Higher Education, Malaysia. TAMU/LBMS-Applications Laboratory provided mass spectrometric support. The NMR instrumentation at Texas A&M University was supported by a grant from the National Science Foundation (DBI-9970232) and the Texas A&M University System. We thank Dr. J. Reibenspies at TAMU for the crystallographic analysis.

■ REFERENCES

(1) (a) Conte, L. L.; Chothia, C.; Janin, J. *J. Mol. Biol.* **1999**, *285*, 2177. (b) Keskin, O.; Gursoy, A.; Ma, B.; Nussinov, R. *Chem. Rev.* **2008**, *108*, 1225.

(2) (a) Lao, B. B.; Grishagin, I.; Mesallati, H.; Brewer, T. F.; Olenyuk, B. Z.; Arora, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2014**, *111*, 7531. (b) Tosovska, P.; Arora, P. S. *Org. Lett.* **2010**, *12*, 1588. (c) Lao, B. B.; Drew, K.; Guarracino, D. A.; Brewer, T. F.; Heindel, D. W.; Bonneau, R.; Arora, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 7877.

(3) Oh, M.; Lee, J. H.; Wang, W.; Lee, H. S.; Lee, W. S.; Burlak, C.; Im, W.; Hoang, Q. Q.; Lim, H.-S. *Proc. Natl. Acad. Sci. U.S.A.* **2014**, *111*, 11007.

(4) Jung, K.-Y.; Vanommeslaeghe, K.; Lanning, M. E.; Yap, J. L.; Gordon, C.; Wilder, P. T.; MacKerell, A. D., Jr.; Fletcher, S. *Org. Lett.* **2013**, *15*, 3234.

(5) German, E. A.; Ross, J. E.; Knipe, P. C.; Don, M. F.; Thompson, S.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **2015**, *54*, 2649.

(6) Sutherell, C. L.; Thompson, S.; Scott, R. T. W.; Hamilton, A. D. *Chem. Commun.* **2012**, *48*, 9834.

(7) Wyrembak, P. N.; Hamilton, A. D. *J. Am. Chem. Soc.* **2009**, *131*, 4566.

(8) Ko, E.; Liu, J.; Burgess, K. *Chem. Soc. Rev.* **2011**, *40*, 4411.

(9) (a) Ko, E.; Liu, J.; Perez, L. M.; Lu, G.; Schaefer, A.; Burgess, K. *J. Am. Chem. Soc.* **2011**, *133*, 462. (b) Xin, D.; Ko, E.; Perez, L. M.; Ioerger, T. R.; Burgess, K. *Org. Biomol. Chem.* **2013**, *11*, 7789.

(10) (a) Raghuraman, A.; Xin, D.; Perez, L. M.; Burgess, K. *J. Org. Chem.* **2013**, *78*, 4823. (b) Raghuraman, A.; Ko, E.; Perez, L. M.; Ioerger, T. R.; Burgess, K. *J. Am. Chem. Soc.* **2011**, *133*, 12350.

(11) Xin, D.; Perez, L. M.; Ioerger, T. R.; Burgess, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 3594.

(12) Xin, D.; Holzenburg, A.; Burgess, K. *Chem. Sci.* **2014**, *5*, 4914.

(13) (a) Bestmann, H. J. *Angew. Chem., Int. Ed.* **1977**, *16*, 349. (b) Schobert, R.; Dietrich, M.; Mullen, G.; Urbina-Gonzalez, J.-M. *Synthesis* **2006**, 3902. (c) Schobert, R. *Org. Synth.* **2005**, *82*, 140.

(14) (a) Xin, D.; Burgess, K. *Org. Lett.* **2014**, *16*, 2108. (b) Li, X.; Taechalertpaisarn, J.; Xin, D.; Burgess, K. *Org. Lett.* **2015**, *17*, 632.

(15) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.

(16) Subiros-Funosas, R.; Prohens, R.; Barbas, R.; El-Faham, A.; Albericio, F. *Chem.—Eur. J.* **2009**, *15*, 9394.

(17) Driver, R. W.; Hoang, H. N.; Abbenante, G.; Fairlie, D. P. *Org. Lett.* **2009**, *11*, 3092.

DOI: 10.1021/acs.joc.5b00300
J. Org. Chem. 2015, 80, 4450−4458