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Beyond the Diketopiperazine Family with Alternatively Bridged Brevianamide F Analogues

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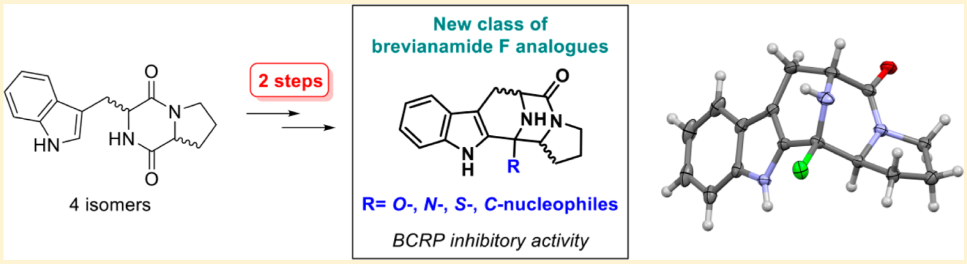
Supporting Information



ABSTRACT: A method for the preparation of 3,5-bridged piperazin-2-ones from a tryptophan−proline-based diketopiperazine is described using diphosgene to induce the ring closure. Density functional theory calculations were conducted to study the mechanism of this C−C bond formation. Several derivatives of the thus obtained α-chloroamine were synthesized by substitution of the chlorine atom using a range of *O*-, *N*-, *S*-, and *C*-nucleophiles. This novel class of brevianamide F analogues possess interesting breast cancer resistance protein inhibitory activity.

INTRODUCTION

Many naturally occurring diketopiperazines have a rather complex and bridged structure.[1] The cyclo(L-Trp, L-Pro) skeleton of **1a** is present in several complex fungal metabolites such as brevianamides (**2**),[2] fumitremorgins (**3**),[3] and (spiro)-tryprostatins (**4**, **5**).[4] Numerous of these fungal metabolites possess interesting biological activities. Demethoxyfumitremorgin C has gained a lot of interest as an anticancer lead.[4a,5] As can be seen in Figure 1, the envisaged compounds are annulated (**3**) or spiroannulated (**2**, **4**) and thus possess an extra bridging structure (Figure 1). The introduction of an extra ring system in these compounds increases the conformational rigidity, which leads to a higher selectivity toward target proteins.

Our research group is interested in studying the structural simplification of complex diketopiperazine (DKP)-based natural products to readily obtainable analogues while maintaining biological activity.[6] Serendipitously, we obtained a novel bridged scaffold which is easy to make. The compound is relevant to medicinal chemistry, as it possesses a stable α-chloroamine, is easily amenable to further modification, and has interesting stereochemical properties.

The 3,5-bridged piperazine moiety in this novel scaffold represents an alternative bridging structure for the tryptophan−proline-based diketopiperazine scaffold.

This compound was discovered during our studies on brevianamide F or cyclo(L-Trp, L-Pro) (**1a**) as a lead scaffold for the construction of bioinspired small molecules.[7] The procedure for the formation of this 3,5-bridged piperazin-2-one derived from cyclo(Trp, Pro) shows a resemblance to the Vilsmeier−Haack reaction. Previously, the construction of diaza-bridged heterocycles had only been achieved by means of an *N*-acyliminium Pictet−Spengler reaction, which prevents further modification at the bridgehead.[8]

The newly obtained bridged structure includes the remarkable feature of a chloro substituent α to nitrogen, a structural unit which is normally unstable. This bridgehead chlorine atom allows further diversification via substitution of the halogen. Using several nucleophiles, a series of derivatives were obtained. A preliminary bioactivity screening of a small subset of compounds has revealed interesting breast cancer resistance protein (BCRP) inhibitory activity.

RESULTS AND DISCUSSION

The synthesis of the different isomers of diketopiperazine **1** was performed using standard protocols (Scheme 1). The carbobenzyloxy (Cbz)-protected tryptophan **7** was coupled with proline methyl ester hydrochloride (ProOMe·HCl) **8** in

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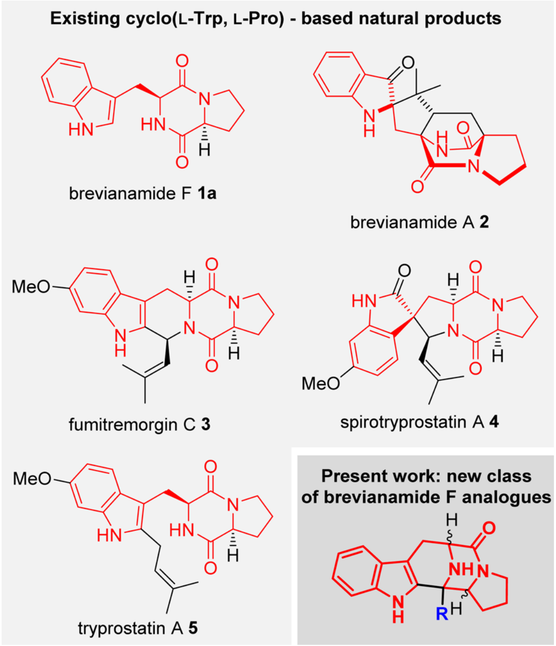


Figure 1. Fungal metabolites containing the cyclo(L-Trp, L-Pro) moiety.

the presence of *N*-ethyl-*N*′-(3-(dimethylamino)propyl)-carbodiimide hydrochloride (EDC·HCl).[9] Carbobenzyloxy-protected D-tryptophan **7a** was obtained by treating the commercially available D-tryptophan **6** with benzyl chloroformate (Cbz-Cl) in an aqueous solution of potassium carbonate and sodium bicarbonate.[10] Subsequent hydrogenolysis of the crude dipeptide **9** with Pd/C under a H_2 atmosphere resulted in the deprotection of tryptophan. For the L,D- and D,L-isomers, spontaneous cyclization toward the piperazine-2,5-dione **1** occurred. Transformation of the *cis*-fused isomers into diketopiperazine **1** required stirring in ammonia in methanol (7 N solution).

During our studies to synthesize simplified DKP analogues, cyclo(D-Trp, L-Pro) **1d** was reacted with triphosgene in the presence of *N*,*N*-diisopropylethylamine (DIPEA), to assess the possibility of introducing a carbonyl bridge between the amide N and the indole group. However, another, unknown, compound was formed during this reaction and was isolated by pTLC. Mass spectral analysis and NMR studies indicated the formation of α-chloroamine **12d**. Its structure was confirmed by X-ray analysis (Scheme 2).

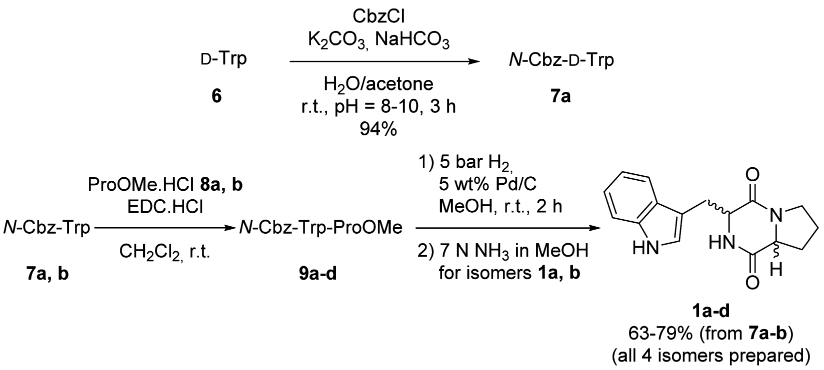
It is assumed that formation of this α-chloroamine **12d** proceeds via a Vilsmeier−Haack-type reaction. We propose that the reaction of triphosgene (or diphosgene) with the amide function of **1** leads to an intermediate imidoyl chloride, **10** (Scheme 2), which is followed by an electrophilic aromatic substitution of the indole moiety with the imidoyl chloride. The latter transformation could be started via nucleophilic attack by either the C2 (pathway a) or the C3 (pathway b) atom of the indole function. C3 attack would lead to an intermediate spiroindolenine (**int-b**), which undergoes a 1,2-shift, giving rise to product **11**, which in its turn would readily lose a proton, affording α-chloroamine **12d**.

Although most literature precedents suggest that the more favorable 6-endo-trig cyclization (pathway a)[11] may be preferred over the less favorable 5-endo-trig cyclization (pathway b), evidence for the formation of a spiroindolenine intermediate (**int-b**) can be found as well.[12] Both pathways were studied by density functional theory (DFT) calculations. Gibbs free energy profiles for the involved transformation are shown in Figure 2. For both pathways, two different transition states—*exo* and *endo*—were found, leading to two different protonated α-chloroamines **11**, which both give rise to the α-chloroamine **12d** after deprotonation.

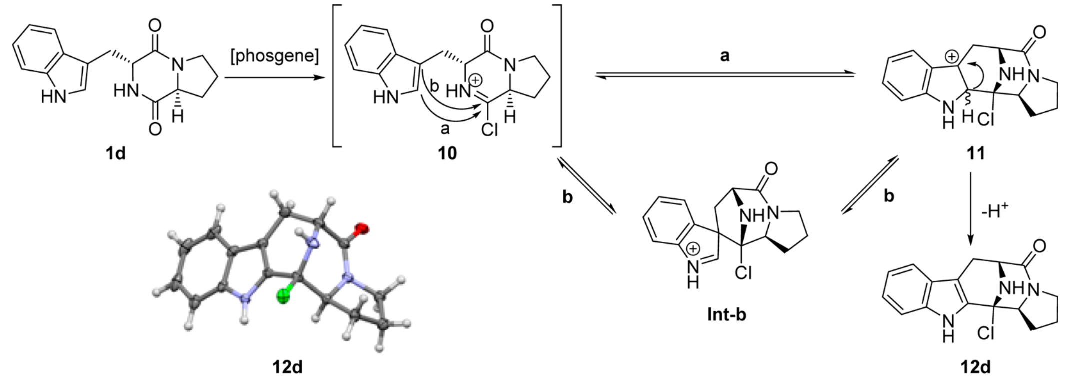
Free activation energies show that pathway a (direct attack by the C2 atom) is the kinetically preferred route, via **TS-a-endo** ($\Delta G^{\ddagger}$ = 58.2 kJ/mol at the M06-2X/6-31+G(d,p) level of theory). Product **11-endo** is the kinetically preferred compound and is quickly deprotonated toward the neutral α-chloroamine **12d** upon formation. Therefore, equilibration of **11-endo** via **10** to the thermodynamically preferred spiroindolenines **int-b** (pathway b, via C3 attack) is not feasible. Moreover, various attempts to model the necessary 1,2-shift (via **TS-b′**) between an intermediate spiroindolenine (**int-b**) and the protonated product **11** failed, as was previously found by Maresh et al. as well.[11b] Presumably, if the intermediate spiroindolenine **int-b** would be formed, it would not undergo a 1,2-shift with formation of the protonated α-chloroamine **11** under the current reaction conditions since this would imply the involvement of a high-energy intermediate. Therefore, any formed **int-b** would equilibrate toward **11-endo** via **10**. It can thus be concluded that α-chloroamine **12d** is most likely formed via direct attack by the C2 atom of the indole function and not via C3 attack followed by a 1,2-shift.

The reaction suffered from low yields, partly due to incomplete conversion of cyclo(D-Trp, L-Pro) **1d**. To improve the conversion, longer reaction times and higher temperatures were evaluated (see Table 1 in the Supporting Information). A

Scheme 1. Synthesis of Cyclo(Trp, Pro) 1a−d



Scheme 2. Reaction of Piperazine-2,5-dione 1d with Triphosgene (or Diphosgene) to α-Chloroamine 12d and X-ray Structure of 12d[a]



[a]Thermal ellipsoid contour probability level 50%.

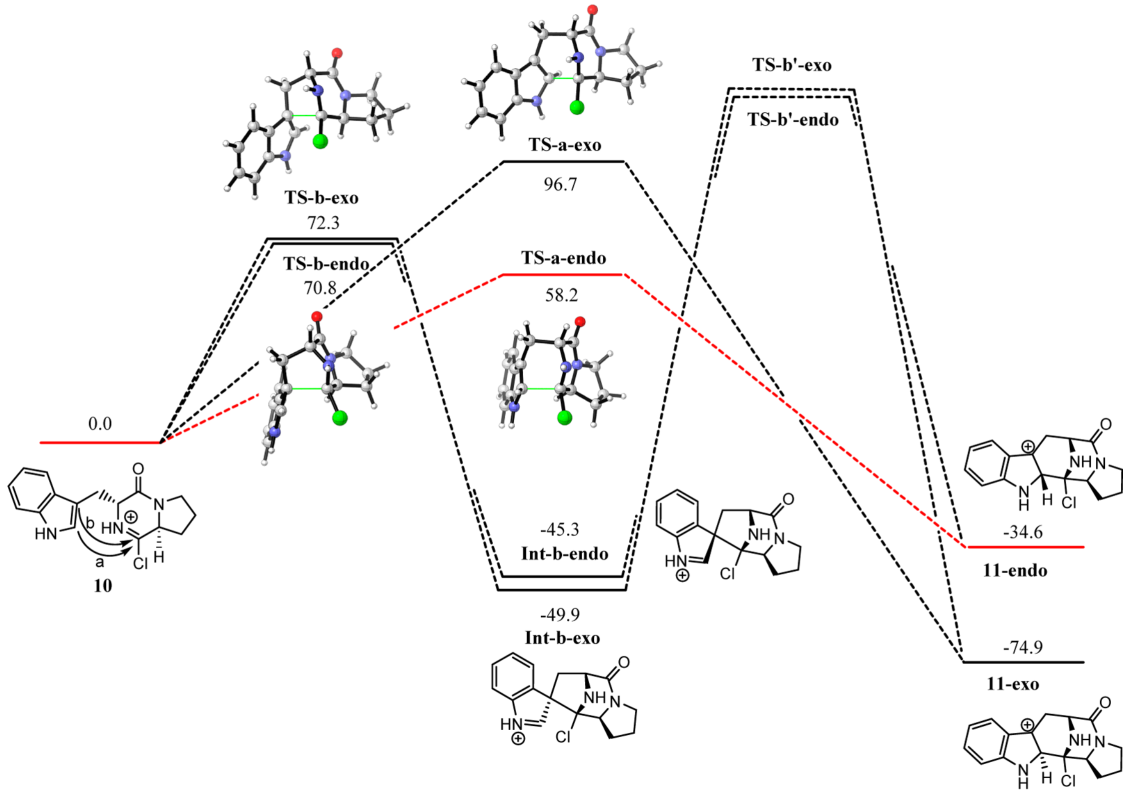


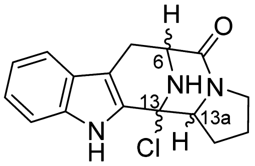
Figure 2. Free energy profiles (kJ/mol) for the reaction of the intermediate imidoyl chloride **10** to the protonated α-chloroamine **11** (PCM (ε = 8.93), M06-2X/6-31+G(d,p)).

run with a larger excess of triphosgene was also attempted. These modifications did, however, not lead to a dramatic increase in the formation of **12d**. The addition of additional base was detrimental to the reaction.

Diphosgene was evaluated as an alternative source of phosgene and gave full conversion. Nevertheless, a significant amount of side product, formed by reaction between DIPEA and excess tri- or diphosgene, impeded the purification, resulting in low yields. This side product was identified as 1,3-diethyl-1,3-diisopropylurea, formation of which was confirmed by the mixing of DIPEA with diphosgene. Several other bases were tested to prevent the formation of this side product, and although reaction took place, complex mixtures were obtained. Only K_2CO_3 gave satisfactory results. Phosphoric trichloride ($POCl_3$), known to react with amides to form imidoyl chlorides and therefore used in Vilsmeier−Haack reactions,[13] was examined as an alternative electrophile under similar reaction conditions. Its use did not result in an analogous reaction.

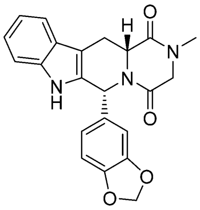
The reaction was also performed in the absence of base. Considering the proposed reaction mechanism, no base is needed. When conducted at room temperature, no conversion was detected. Under reflux conditions, the reaction proceeded partly and the formation of the urea was avoided. Finally, full conversion was achieved by using an excess of diphosgene. Under these conditions, α-chloroamine **12d** was obtained as the major product. Isolation by column chromatography lowered the final yield due to the polarity of the compound.

The different isomers of cyclo(Trp, Pro) **1** were subjected to the reaction conditions to afford the pentacycles **12a−d**.



(6*S*,13*R*,13a*S*)-**12a** 40%
(6*R*,13*S*,13a*R*)-**12b** 46%
(6*S*,13*R*,13a*R*)-**12c** 24%
(6*R*,13*S*,13a*S*)-**12d** 50%

Since diastereomer **12d** gave the best isolated yield, it was chosen as a substrate to develop a small library of compounds. In cyclo(Trp, Pro) natural products, typically the *cis* configuration is present, originating from the natural L-amino acids. However, compounds containing unnatural D-amino acids have also proven to possess biological activity. Tadalafil (**13**), for example, a commercially available drug used for the treatment of erectile dysfunction, contains a D-tryptophan unit.[14]



Tadalafil **13**

In a typical Vilsmeier−Haack reaction, the α-chloroamines are unstable and undergo hydrolysis. Our newly formed products, however, did not readily hydrolyze to give the corresponding eight-membered ring expanded system. Hydrolysis of the bridged structure under acidic conditions proved unsuccessful with full recovery of the starting material. Using sodium hydroxide, compound **14a** was isolated. The particular stability of the α-chloroamine can be attributed to its bridged structure.

Exposing **12d** to nucleophiles such as methanol, water, or allylamine under neutral conditions gave no conversion of the starting material. Nevertheless, related compounds are known to exhibit a remarkable reactivity toward nucleophiles under basic conditions.[15] Therefore, in the next step, compound **12d** was reacted with several *O*-, *N*-, and *S*-nucleophiles in the presence of base or an alkyllithium reagent (Scheme 3 and Table 2 in the Supporting Information). These reactions proceeded smoothly. Since no protective groups were used, 3 equiv of nucleophile was added. However, good conversion was also achieved using only 1.5 equiv of nucleophile in particular cases (**14d**, **14i**, and **14j**). Unfortunately, separation of the desired products from the excess reagent and the remaining substrate proved tedious, due to the polar nature of the materials. Therefore, when the compounds were not immediately obtained in pure form after workup, they were only recovered in low yields by pTLC. Poor solubility of some derivatives also lowered the isolated yields.

The reported structures are the first examples of a new class of brevianamide F analogues bearing the 3,5-bridged piperazin-2-one core. A preliminary evaluation of the bioactivity of these interesting materials was conducted. The antimicrobial activity of compounds **12d** and **14b** was tested against a panel of four bacterials strains (Gram-negative *Escherichia coli* LMG 8063 and *Klebsiella pneumonia* LMG 2095 and Gram-positive *Staphylococcus aureus* LMG 8064 and *Bacillus substilis* LMG 13579). No antimicrobial effect was observed on the basis of visual assessment of turbidity caused by bacterial growth.

A subset of compounds was tested against different targets that were chosen on the basis of the interest of the laboratory for those targets[16] and on the basis of biological activities displayed by natural product analogous to these compounds.

α-Chloroamine **12d** and two derivatives, **14c** or **14d** and **14i**, were submitted to competitive binding assays against a set of receptors (Table 1, entries a−e). No significant binding to these receptors could be detected.

The compounds were also tested for their inhibitory activity against the phosphodiesterase type 5 (PDE5) enzyme, which plays an important role in the cardiovascular system (Table 1, entry f).[17] Tadalafil **13** is a potent inhibitor of these enzymes, and bears structural resemblance to the tested compounds.[18] Unfortunately, α-chloroamine **12d** and derivatives **14c** and **14i** exhibit a very low potency for PDE5 inhibtion. The best result was obtained for **14i**, containing an aromatic benzyl side chain. Of the tested compounds, **14i** indeed displays the most resemblance to the 1,3-benzodioxole substituent of tadalafil **13**.

The fungal metabolite tryprostatin A (**5**) was identified as an inhibitor of tubulin polymerization and thus prevents cell cycle progression at the M-phase.[19] Compounds **12d**, **14d**, and **14i** do not impair the microtubule assembly at the tested concentrations (Table 1, entry g).

Several diketopiperazines, including fumitremorgin C (**3**) and analogues, have been reported to reverse multidrug resistance in cells transfected with the BCRP.[20] The BCRP is a transmembrane transporter that contributes to the resistance of cancer cells to chemotherapeutic agents such as mitoxantrone, topotecan, and methotrexate, by removing these substances from the cell. Interestingly, compounds **14d** and **14i** display a significant inhibition of BCRP (46.5% and 40.6%

Scheme 3. Derivatization of 12d with Different Nucleophiles

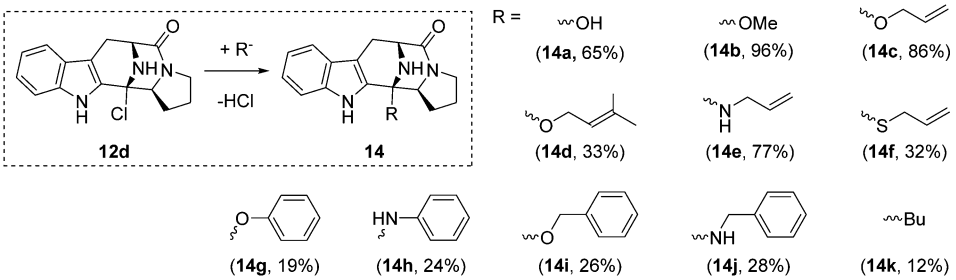
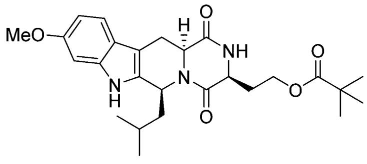


Table 1. Screening of Different Targets[j]

	12d		14c		14d		14i		13	
a **α2 (non-selective)[a],[b]**	60 nM -7.1	6 μM -5.5	60 nM -8.4	60 nM -13.1			6 μM -9.6	60 nM -7.0		
b **D1[a],[c]**	2.5 μM -6	25 μM 2			2.5 μM 3	2.5 μM -6	25 μM 2	2.5 μM 3		
c **N neuronal α7[a],[d]**	7 μM 2	70 μM -15			7 μM -8	70 μM -7	6.1 μM -8	61 μM -4		
d **N muscle-type[a],[e]**	20 μM 5	0.2 nM 7			20 μM -6	0.2 nM -3	17 μM 0	0.17 nM -5		
e **Serotonin 5-HT1 (non-selective)[f]**	11 μM 0	0.11 nM 3			11 μM 11	0.11 nM 8	9.5 μM -4	95 μM -3		
f **PDE5(h) (non-selective)[g]**	0.7 μM -1.0	70 μM 7.2	0.7 μM 0.0	70 μM 16.8			0.7 μM 0.9	70 μM 18.7	0.7 μM 101.8	70 μM 100.9
g **Tubulin polymerization[h]**	12 nM -8	0.12 mM -14			12 nM -10	12 nM -8	0.12 mM -14	12 nM -10		
h **BCRP (h) inhibition[i]**	5 μM 0.1	50 μM 10.8			5 μM 21.5	50 μM 46.5	4.3 μM 6.9	43 μM 40.6		

[a] Antagonist radioligand. [b] Reference: yohimbine (IC_{50} = 58.7 nM). [c] Reference: SCH 23390 (IC_{50} = 0.242 nM). [d] Reference: α-bungarotoxin (IC_{50} = 0.7 nM). [e] Reference: α-bungarotoxin (IC_{50} = 2 nM). [f] Reference: serotonin (5-HT) (IC_{50} = 0.0011 μM). [g] Reference: dipyridamole (IC_{50} = 0.7 μM). [h] Reference: vinblastine (IC_{50} = 1200 nM). [i] Reference: KO143 (IC_{50} = 480 nM). [j] The values express the percentage inhibition (of the control). All assays were run by Cerep, France. For more details, see the Supporting Information. All values are the mean of two replicates. The test concentrations that were used are based on the IC_{50} values of the reference compounds and the 100-fold or 10-fold values thereof.

at 50 and 43 μM, respectively) (Table 1, entry h). The presence of a more bulky side chain replacing the chlorine atom is required for activity, since **12d** does not display a significant degree of inhibition. The IC_{50} values of **14d** and **14i** are moderate compared to that of the reference compound Ko 143 (**15**), also a diketopiperazine.



Ko 143 (**15**)

However, the novel scaffold allows further modification with other nucleophiles (Figure 3, modification a) and isomers of **12** (Figure 3, modification b) and modifications to the amino acids, e.g., substitution of tryptophan (Figure 3, modification c), which may lead to more active compounds. Further work is needed to validate the more elaborate scaffolds.

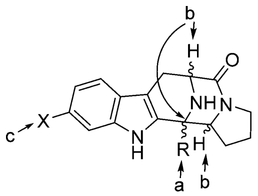


Figure 3. Possible sites for modification of the novel 3,5-bridged structure.

CONCLUSIONS

A method for the preparation of 3,5-bridged piperazin-2-ones containing an α-chloroamine functionality from cyclo(Trp, Pro) was presented using diphosgene for the formation of the C−C bond for the pentacyclic scaffold. DFT calculations suggest that the α-chloroamine is formed by direct attack by the C2 atom of the indole group and not by C3 attack and a subsequent 1,2-shift. Substitution of the thus obtained α-chloroamine pentacycle offers a new avenue toward synthetic analogues of brevianamides, fumitremorgins, and (spiro)-tryprostatins. To illustrate this opportunity, a small library of decorated pentacycles was synthesized using a range of *O*-, *N*-, *S*-, and *C*-nucleophiles. A preliminary bioactivity screening of some of the newly developed diketopiperazines revealed significant inhibition of BCRP. Structural modifications to obtain higher BCRP inhibitory potency are possible, as the presence of the α-chloroamine provides an easy way to decorate the novel pentacyclic framework. Besides, other isomers are easily accessible.

EXPERIMENTAL SECTION

General Remarks. High-resolution ^1H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were recorded. All chemical shifts (δ) are given in parts per million relative to TMS. Data are reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and integration. The compounds were dissolved in deuterated solvents, and the solvent used is indicated for each compound. Reaction progress was monitored using LC−MS. R_f values were obtained by using thin-layer chromatography (TLC) (silica gel 60 F_{245}). High-resolution mass spectra were obtained with a time-of-flight (TOF) mass spectrometer, equipped with an ESI/APCI multimode source. Infrared spectra were recorded on an FT-IR spectrophotometer with an ATR (attenuated total reflectance) accessory, and the $\tilde{\nu}$ values are given in inverse centimeters. All compounds were analyzed in neat form.

Purification of reaction mixtures by normal-phase column chromatography was performed using silica gel (particle size 0.035−0.070 mm, pore diameter ca. 6 nm) or by preparative thin-layer chromatography (pTLC). Reversed-phase chromatrography was performed with a C18 RP cartridge. Dry CH_2Cl_2 was freshly distilled from CaH_2, and dry THF was distilled from sodium. Reagents were used as received from the supplier unless stated otherwise.

Synthesis of *N*-Cbz-D-Trp (7a).[10] D-Tryptophan **6** (1 equiv, 49 mmol, 10.0 g) was suspended in H_2O (300 mL), and K_2CO_3 (2.0 equiv, 98 mmol, 13.5 g) and $NaHCO_3$ (1.0 equiv, 49 mmol, 4.11 g) were added. The addition of acetone (40 mL) gave a clear solution. Cbz-Cl (1.25 equiv, 61 mmol, 8.7 mL) was added slowly to the solution while it was being cooled with an ice−water bath. Next, the mixture was warmed to 30 °C. After being stirred at 30 °C for 3 h, the mixture was extracted with Et_2O (50 mL). The aqueous layer was acidified to a pH of 2 with 2 M aqueous HCl. The resulting precipitate was extracted by ethyl acetate. The organic phase was washed with H_2O (100 mL) and dried over magnesium sulfate, and the solids were removed by filtration. Concentration of the mixture under reduced pressure resulted in a viscous oil. The oil was redissolved in CH_2Cl_2, and the solution was concentrated in vacuo. **7a** was obtained as a white powder (15.6 g, 94%) and was used in the next step without further purification.

General Procedure for Cyclo(Trp, Pro) 1. Proline methyl ester **8** (1 equiv, 7.64 g, 46 mmol) was dissolved in dry CH_2Cl_2 (350 mL), and *N*-[(benzyloxy)carbonyl]tryptophan **7** (1 equiv, 15.6 g, 46 mmol) and EDC·HCl (1 equiv, 8.82 g, 46 mmol) were subsequently added under a nitrogen atmosphere. The mixture was stirred at room temperature for 24 h and was then washed three times with 1 M HCl (100 mL) and 1 M aqueous $NaHCO_3$ (100 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced presssure, yielding dipeptide **9**.[9]

To a solution of dipeptide **9** in MeOH (250 mL) was added 5 wt % Pd/C. The reaction mixture was stirred under 5 atm of H_2 for 2 h at room temperature. The Pd/C catalyst was removed by filtration through a Celite pad. In the case of the D,L- and L,D-isomers, the methanolic solution was stirred at room temperature until ring closure was complete. In the case of the *cis*-fused isomers, ammonia in methanol was added to induce ring formation. The filtrate was concentrated in vacuo to give the crude diketopiperazine. The pure product **1** was obtained after recrystallization from methanol as white crystals. The structure of the products was confirmed by comparison of the spectroscopic data with literature values.[4b,21]

General Procedure A: Synthesis of α-Chloroamines 12a−d. Diketopiperazine **1** (1 equiv) was suspended in dry CH_2Cl_2 and cooled with an ice bath to 0 °C under a nitrogen atmosphere. Diphosgene (3 equiv), dissolved in dry CH_2Cl_2, was added dropwise to the suspension. The mixture was heated to reflux. After complete conversion the organic phase was washed with saturated $NaHCO_3$ solution and with water. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. Purification of the residue by chromatography provided the desired products.

(6S,13R,13aS)-13-Chloro-1,2,3,6,7,12,13,13a-octahydro-5H-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-b]indol-5-one ***(12a)***. Using general procedure A on a 0.7 mmol scale, compound **12a** was obtained after pTLC: yield 40% (0.084 g); white powder; R_f = 0.20 (CH_2Cl_2/4% MeOH); mp 224−230 °C; $[\alpha]_D^{25}$ = +102.8 (c = 0.51 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 1.76−2.16 (m, 4H), 2.71 (s, 1H), 2.92−3.01 (m, 1H), 3.05 (d, J = 16.4 Hz, 1H), 3.18 (dd, J = 16.4 Hz, J = 5.9 Hz, 1H), 3.79 (dd, J = 11.0 Hz, J = 5.0 Hz, 1H), 4.04−4.15 (m, 1H), 4.23 (d, J = 5.9 Hz, 1H), 7.14 (dd, J = 7.7 Hz, J = 7.7 Hz, 1H), 7.24 (dd, J = 7.7 Hz, J = 7.7 Hz, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 8.25 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.2, 24.9, 28.2, 44.4, 58.1, 68.5, 77.4, 109.3, 111.5, 119.3, 120.4, 123.6, 126.5, 134.3, 136.0, 169.3 ppm; IR $\tilde{\nu}$ = 3151 (NH), 1624 (C═O); MS (ES) m/z (rel intens, %) 302 (100) $[M + H]^+$, 304 (35) $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{17}ClN_3O^+$ $[M + H]^+$ 302.1055, found 302.1057.

(6R,13S,13aR)-13-Chloro-1,2,3,6,7,12,13,13a-octahydro-5H-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-b]indol-5-one ***(12b)***. Following general procedure A on a 0.7 mmol scale, compound **12b** was obtained after pTLC: yield 46% (0.097 g); white powder; R_f = 0.22 (CH_2Cl_2/2% MeOH); mp 210−218 °C; $[\alpha]_D^{25}$ = −102.5 (c = 0.38 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 1.76−2.18 (m, 4H), 2.68 (s, 1H), 2.92−3.01 (m, 1H), 3.04 (d, J = 16.5 Hz, 1H), 3.18 (dd, J = 16.5 Hz, J = 6.3 Hz, 1H), 3.79 (dd, J = 10.7 Hz, J = 4.7 Hz, 1H), 4.03−4.15 (m, 1H), 4.23 (d, J = 6.3 Hz, 1H), 7.14 (dd, J = 7.8 Hz, J = 7.8 Hz, 1H), 7.24 (dd, J = 7.8 Hz, J = 7.8 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 8.25 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.3, 24.9, 28.2, 44.4, 58.2, 68.5, 77.0, 109.3, 111.5, 119.3, 120.4, 123.6, 126.6, 134.3, 136.0, 169.3 ppm; IR $\tilde{\nu}$ = 3222 (NH), 1613 (C═O), 1446; MS (ES) m/z (rel intens, %) 302 (100) $[M + H]^+$, 304 (35) $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{17}ClN_3O^+$ $[M + H]^+$ 302.1055, found 302.1062.

(6S,13R,13aR)-13-Chloro-1,2,3,6,7,12,13,13a-octahydro-5H-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-b]indol-5-one ***(12c)***. Using general procedure A on a 0.7 mmol scale, compound **12c** was obtained after pTLC: yield 24% (0.051 g); white powder; R_f = 0.17 (CH_2Cl_2/4% MeOH); mp 240−246 °C; $[\alpha]_D^{25}$ = +115.3 (c = 0.50 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 1.68−2.20 (m, 4H), 2.69 (s, 1H), 2.92−3.02 (m, 1H), 3.05 (d, J = 16.5 Hz, 1H), 3.19 (dd, J = 16.5 Hz, J = 6.3 Hz, 1H), 3.79 (dd, J = 11.0 Hz, J = 5.0 Hz, 1H), 4.03−4.16 (m, 1H), 4.24 (d, J = 6.3 Hz, 1H), 7.14 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H), 7.25 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 8.20 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.2, 24.9, 28.2, 44.4, 58.1, 68.5, 77.4, 109.3, 111.5, 119.3, 120.4, 123.6, 126.6, 134.3, 136.0, 169.3 ppm; IR $\tilde{\nu}$ = 3171 (NH), 1624 (C═O), 1451; MS (ES) m/z (rel intens, %) 302 (100) $[M + H]^+$, 304 (35) $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{17}ClN_3O^+$ $[M + H]^+$ 302.1055, found 302.1065.

(6R,13S,13aS)-13-Chloro-1,2,3,6,7,12,13,13a-octahydro-5H-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-b]indol-5-one ***(12d)***. Following general procedure A on a 10 mmol scale, compound **12d** was obtained after column chromatography: yield 50% (1.51 g); white crystals; R_f = 0.25 (EtOAc/petroleum ether (6:4) + 4% Et_3N); mp 248−250 °C; $[\alpha]_D^{20}$ = −115.3 (c = 0.48 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 1.78−2.19 (m, 4H), 2.70 (s, 1H), 2.93−3.02 (m, 1H), 3.05 (d, J = 16.5 Hz, 1H), 3.20 (dd, J = 16.5 Hz, J = 6.6 Hz, 1H), 3.80 (dd, J = 11.0 Hz, J = 5.0 Hz, 1H), 4.05−4.16 (m, 1H), 4.24 (d, J = 6.6 Hz, 1H), 7.15 (dd, J = 7.7 Hz, J = 7.7 Hz, 1H), 7.25 (dd, J = 7.7 Hz, J = 7.7 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 8.14 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.3, 24.9, 28.2, 44.4, 58.2, 68.5, 77.0, 109.3, 111.5, 119.3, 120.4, 123.6, 126.6, 134.3, 136.0, 169.3 ppm; IR $\tilde{\nu}$ = 3150 (NH), 1621 (C═O), 1461, 1450; MS (ES) m/z (rel intens, %) 302 (100) $[M + H]^+$, 304 (33) $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{17}ClN_3O^+$ $[M + H]^+$ 302.1055, found 302.1067.

Procedure for the Synthesis of (6*R*,13*S*,13a*S*)-13-Hydroxy-1,2,3,6,7,12,13,13a-octahydro-5*H*-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-*b*]indol-5-one (14a). α-Chloroamine **12d** (1 equiv, 1 mmol, 302 mg) was suspended in 10 mL of 2 M aqueous NaOH and refluxed until the conversion was complete. The aqueous phase was then neutralized with 2 M aqueous HCl (10 mL), resulting in a suspension which was extracted three times with chloroform (10 mL). The white precipitate moved to the organic phase (suspension). The layers were separated, and the organic phase was filtered off to yield compound **14a** as a white powder (65%): yield 65% (184 mg); white powder; mp >260 °C; $[\alpha]_D^{20}$ = +92.8 (c = 0.42 in DMF); ^1H NMR (400 MHz, DMSO-d_6) δ = 1.21−1.34 (m, 1H), 1.54−1.72 (m, 2H), 2.04−2.13 (m, 1H), 2.81 (dd, J = 15.1 Hz, J = 1.4 Hz, 1H), 2.91 (dd, J = 15.1 Hz, J = 5.1 Hz, 1H), 3.07 (ddd, J = 11.6 Hz, J = 9.3 Hz, J = 9.3 Hz, 1H), 3.17 (ddd, J = 11.6 Hz, J = 9.0 Hz, J = 2.5 Hz, 1H), 3.34 (s, 1H), 3.79 (dd, J = 11.2 Hz, J = 5.1 Hz, 1H), 3.85 (d, J = 5.1 Hz, 1H), 6.48 (s, 1H), 6.93 (ddd, J = 7.7 Hz, J = 7.7 Hz, J = 1.0 Hz, 1H), 7.04 (ddd, J = 7.7 Hz, J = 7.7 Hz, J = 1.0 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 7.7 Hz, 1H), 11.04 (s, 1H) ppm; ^{13}C NMR (100

MHz, DMSO-d_6) δ = 21.7, 26.6, 28.2, 44.7, 56.1, 68.2, 80.1, 108.2, 111.5, 118.1, 118.3, 121.0, 126.1, 133.6, 136.0, 169.9 ppm; IR $\tilde{\nu}$ = 3262 (NH), 1593 (C═O), 1452; MS (ES) m/z (rel intens, %) = 284 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{18}N_3O_2^+$ $[M + H]^+$ 284.1394, found 284.1401.

Procedure for the Synthesis of (6*R*,13*S*,13a*S*)-13-Methoxy-1,2,3,6,7,12,13,13a-octahydro-5*H*-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-*b*]indol-5-one (14b). α-Chloroamine **12d** (1 equiv, 1 mmol, 302 mg) was suspended in MeOH (10 mL). A sodium methoxide solution in MeOH (1 equiv, 1 mmol, 0.25 mL of 4 M solution) was added, and the mixture was refluxed for 2.5 h. Next, the mixture was quenched by the addition of water, and the solvent was concentrated under reduced pressure. The residual white precipitate was redissolved in chloroform (10 mL) and washed three times with water. After the organic phase was dried over MgSO$_4$, the solvent was removed by evaporation to give compound **14b** as a white solid (96%): yield 96% (285 mg); white solid; mp >260 °C; $[\alpha]_D^{20}$ = −69.8 (c = 0.35 in CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.55−1.68 (m, 1H), 1.72−1.86 (m, 1H), 1.92−2.04 (m, 2H), 2.23 (s, 1H), 2.93 (ddd, J = 12.2 Hz, J = 10.1 Hz, J = 4.8 Hz, 1H), 3.02 (dd, J = 15.9 Hz, J = 1.3 Hz, 1H), 3.20 (dd, J = 15.9 Hz, J = 6.5 Hz, 1H), 3.35 (s, 3H), 3.58 (dd, J = 11.8 Hz, J = 4.9 Hz, 1H), 3.94−4.03 (m, 1H); 4.17 (dd, J = 6.5 Hz, J = 1.3 Hz, 1H), 7.13 (ddd, J = 7.8 Hz, J = 7.8 Hz, J = 1.0 Hz, 1H), 7.21 (ddd, J = 7.8 Hz, J = 7.8 Hz, J = 1.0 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 8.09 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ = 21.5, 24.4, 25.5, 43.5, 51.3, 57.8, 66.6, 83.6, 111.2, 111.3, 119.0, 120.0, 122.8, 126.9, 133.2, 136.1, 171.3 ppm; IR $\tilde{\nu}$ = 3150 (NH), 1620 (C═O), 1462; MS (ES) m/z (rel intens, %) = 298 (100) $[M + H]^+$, 595 (75); HRMS (ESI) calcd for $C_{17}H_{20}N_3O_2^+$ $[M + H]^+$ 298.1550, found 298.1556.

General Procedure B: Synthesis of Derivatives 14c−j. The nucleophile (3 equiv, 1.5 mmol, or 1.5 equiv, 0.75 mmol) was dissolved in THF (10 mL) at room temperature. The solution was cooled to 0 °C, and sodium hydride (3 equiv, 1.5 mmol, 60 mg, or 1.5 equiv, 0.75 mmol, 30 mg, respectively, 60% in mineral oil) was added. After the resulting mixture was stirred for 15 min at 0 °C, α-chloroamine **12** (1 equiv, 0.5 mmol, 151 mg) was added to it. The mixture was allowed to warm to room temperature and was kept stirring until the conversion was complete. An ammonia chloride solution (10 mL) and ethyl acetate (15 mL) were added subsequently. The layers were separated, and the aqueous phase was extracted with 10 mL of ethyl acetate. The combined organic phases were washed three times with water (10 mL). The organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to remove the solvent. When necessary, further purification was done by chromatography using (a mixture of) ethyl acetate (and methanol) as the eluent to provide the desired compound.

*(6R,13S,13aS)-13-(Allyloxy)-1,2,3,6,7,12,13,13a-octahydro-5H-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-b]indol-5-one (**14c**).* Using general procedure B with 3 equiv of allyl alcohol, compound **14c** was obtained without further purification: yield 86% (140 mg); yellow powder; mp 258−260 °C; $[\alpha]_D^{20}$ = −28.4 (c = 0.32 in CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.58−1.71 (m, 1H), 1.71−1.83 (m, 1H), 1.91−2.05 (m, 2H), 2.60 (s, 1H), 2.90 (ddd, J = 12.1 Hz, J = 10.3 Hz, J = 4.6 Hz, 1H), 3.01 (dd, J = 15.9 Hz, J = 1.0 Hz, 1H), 3.18 (dd, J = 15.9 Hz, J = 6.4 Hz, 1H), 3.61 (dd, J = 11.7 Hz, J = 4.9 Hz, 1H), 3.92 (ddt, J = 13.7 Hz, J = 5.1 Hz, J = 1.7 Hz, 1H), 3.96 (ddd, J = 12.1 Hz, J = 9.4 Hz, J = 6.1 Hz, 1H), 4.15 (dd, J = 5.1 Hz, J = 1.0 Hz, 1H), 4.31 (ddt, J = 13.7 Hz, J = 4.9 Hz, J = 1.7 Hz, 1H), 5.14 (ddt, J = 10.5 Hz, J = 1.7 Hz, J = 1.7 Hz, 1H), 5.28 (ddt, J = 17.1 Hz, J = 1.7 Hz, J = 1.7 Hz, 1H), 5.92 (dddd, J = 17.1 Hz, J = 10.5 Hz, J = 5.1 Hz, J = 4.9 Hz, 1H), 7.10 (ddd, J = 7.7 Hz, J = 7.7 Hz, J = 0.6 Hz, 1H), 7.18 (ddd, J = 7.7 Hz, J = 7.7 Hz, J = 0.6 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 8.45 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ = 21.5, 24.4, 25.6, 43.6, 57.9, 64.4, 66.7, 83.6, 110.8, 111.4, 115.6, 119.0, 119.9, 122.7, 126.9, 133.6, 135.3, 136.2, 171.4 ppm; IR $\tilde{\nu}$ = 3266 (NH), 1628 (C═O), 1457; MS (ES) m/z (rel intens, %) = 324 (100) $[M + H]^+$, 647 (65); HRMS (ESI) calcd for $C_{19}H_{22}N_3O_2^+$ $[M + H]^+$ 324.1707, found 324.1700.

*(6R,13S,13aS)-13-[(3-Methylbut-2-en-1-yl)oxy]-1,2,3,6,-7,12,13,13a-octahydro-5H-6,13-epiminopyrrolo[1′,2′:1,2]azocino-[4,5-b]indol-5-one (**14d**).* Following general procedure B using 1.5 equiv of prenyl alcohol, **14d** was obtained after purification by reversed-phase chromatography (2 column volumes (CVs) of 9:1 H$_2$O/ACN, over 16 CVs to 6:4 H$_2$O/ACN, then 8 CVs of 6:4 H$_2$O/ACN) as a yellow powder: yield 33% (58 mg); yellow powder; mp 116−124 °C; $[\alpha]_D^{20}$ = −66.5 (c = 0.53 in CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.53 (s, 3H), 1.57−1.70 (m, 1H), 1.73 (s, 3H), 1.71−1.84 (m, 1H), 1.93−2.04 (m, 2H), 2.31 (s, 1H), 2.88−2.96 (m, 1H), 3.02 (d, J = 15.9 Hz, 1H), 3.20 (dd, J = 15.9 Hz, J = 6.0 Hz, 1H), 3.58 (dd, J = 11.8 Hz, J = 4.9 Hz, 1H), 3.90−4.02 (m, 2H), 4.17 (d, J = 6.0 Hz, 1H), 4.27 (dd, J = 11.9 Hz, J = 6.5 Hz, 1H), 5.34 (t, J = 6.5 Hz, 1H), 7.12 (dd, J = 7.7 Hz, J = 7.7 Hz, 1H), 7.21 (dd, J = 7.7 Hz, J = 7.7 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 8.10 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ = 18.1, 21.5, 24.5, 25.6, 25.8, 43.6, 57.9, 60.7, 66.7, 83.4, 110.9, 111.2, 119.0, 119.9, 121.3, 122.7, 126.9, 133.8, 136.1, 136.5, 171.3 ppm; IR $\tilde{\nu}$ = 3252 (NH), 1627 (C═O), 1446; MS (ES) m/z (rel intens, %) = 352 (100) $[M + H]^+$, 703 (30); HRMS (ESI) calcd for $C_{21}H_{26}N_3O_2^+$ $[M + H]^+$ 352.2020, found 352.2029.

*(6R,13R,13aS)-13-(Allylamino)-1,2,3,6,7,12,13,13a-octahydro-5H-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-b]indol-5-one (**14e**).* Using general procedure B using 3 equiv of allylamine, compound **14e** was obtained without further purification: yield 77% (124 mg); yellow powder; mp 206−210 °C; $[\alpha]_D^{20}$ = −28.3 (c = 0.34 in CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.50−1.73 (m, 2H), 1.73−1.88 (m, 1H), 1.88−1.97 (m, 1H), 1.97−2.12 (m, 2H), 2.94 (ddd, J = 12.2 Hz, J = 10.2 Hz, J = 4.6 Hz, 1H), 3.03 (dd, J = 16.1 Hz, J = 1.4 Hz, 1H), 3.02−3.13 (m, 1H), 3.13 (dd, J = 16.1 Hz, J = 6.4 Hz, 1H), 3.39 (ddt, J = 14.6 Hz, J = 6.4 Hz, J = 1.5 Hz, 1H), 3.50 (dd, J = 11.9 Hz, J = 4.6 Hz, 1H), 4.01 (ddd, J = 12.2 Hz, J = 9.5 Hz, J = 6.2 Hz, 1H), 4.18 (dd, J = 6.4 Hz, J = 1.4 Hz, 1H), 5.11 (ddt, J = 10.3 Hz, J = 1.5 Hz, J = 1.5 Hz, 1H), 5.23 (ddt, J = 17.1 Hz, J = 1.5 Hz, J = 1.5 Hz, 1H), 5.92 (dddd, J = 17.1 Hz, J = 10.3 Hz, J = 6.4 Hz, J = 4.8 Hz, 1H), 7.11 [ddd, J = 7.7 Hz, J = 7.7 Hz, J = 1.0 Hz, 1H), 7.19 (ddd, J = 7.7 Hz, J = 7.7 Hz, J = 1.0 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H), 8.20 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ = 21.5, 25.1 (2 carbons), 43.2, 44.7, 57.1, 67.1, 67.8, 110.0, 111.2, 115.6, 118.8, 119.7, 122.5, 127.3, 134.9, 135.6, 136.9, 170.9 ppm; IR $\tilde{\nu}$ = 3273 (NH), 1613 (C═O), 1455; MS (ES) m/z (rel intens, %) = 323 (100) $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{23}N_4O^+$ $[M + H]^+$ 323.1866, found 323.1881.

*(6R,13S,13aS)-13-(Allylthio)-1,2,3,6,7,12,13,13a-octahydro-5H-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-b]indol-5-one (**14f**).* Using general procedure B using 3 equiv of allyl mercaptan, **14f** was obtained after purification by pTLC as a white powder: yield 32% (55 mg); white powder; R_f = 0.22 (EtOAc); mp 136−140 °C; $[\alpha]_D^{20}$ = −165.26 (c = in CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.63−1.76 (m, 1H), 1.76−1.87 (m, 1H), 1.91−1.99 (m, 1H), 1.99−2.07 (m, 1H), 2.45 (s, 1H), 2.95 (ddd, J = 12.2 Hz, J = 10.2 Hz, J = 4.6 Hz, 1H), 3.01 (dd, J = 16.0 Hz, J = 1.3 Hz, 1H), 3.02 (ddt, J = 13.6 Hz, J = 7.4 Hz, J = 1.2 Hz, 1H), 3.16 (dd, J = 16.0 Hz, J = 6.5 Hz, 1H), 3.29 (ddt, J = 13.3 Hz, J = 7.0 Hz, J = 1.2 Hz, 1H), 3.58 (dd, J = 11.9 Hz, J = 4.7 Hz, 1H), 3.99 (ddd, J = 12.2 Hz, J = 9.5 Hz, J = 6.3 Hz, 1H), 4.06 (dd, J = 6.5 Hz, J = 1.3 Hz, 1H), 5.01 (ddt, J = 9.9 Hz, J = 1.2 Hz, J = 1.2 Hz, 1H), 5.04 (ddt, J = 17.0 Hz, J = 1.2 Hz, J = 1.2 Hz, 1H), 5.79 (dddd, J = 17.0 Hz, J = 9.9 Hz, J = 7.4 Hz, J = 7.0 Hz, 1H), 7.13 (ddd, J = 7.8 Hz, J = 7.8 Hz, J = 1.1 Hz, 1H), 7.21 (ddd, J = 7.8 Hz, J = 7.8 Hz, J = 1.1 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 8.16 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ = 21.7, 24.8, 26.2, 31.9, 43.1, 55.9, 63.1, 67.0, 110.4, 111.2, 117.9, 118.9, 120.0, 122.7, 127.2, 134.0, 134.3, 135.5, 170.9 ppm; IR $\tilde{\nu}$ = 3262 (NH), 1614 (C═O), 1448; MS (ES) m/z (rel intens, %) = 340 (100) $[M + H]^+$, 679 (25); HRMS (ESI) calcd for $C_{19}H_{22}N_3OS^+$ $[M + H]^+$ 340.1478, found 340.1490.

*(6R,13S,13aS)-13-Phenoxy-1,2,3,6,7,12,13,13a-octahydro-5H-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-b]indol-5-one (**14g**).* Following general procedure B using 3 equiv of phenol, **14g** was obtained as the insoluble residue from rinsing the crude with acetone and

methanol: yield 19% (55 mg); white powder; mp 136−140 °C; $[\alpha]_D^{20}$ = −34.1 (c = 0.26 in THF); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.74−1.87 (m, 1H), 1.88−2.10 (m, 3H), 2.79 (d, J = 15.7 Hz, 1H), 2.87 (ddd, J = 11.7 Hz, J = 10.2 Hz, J = 4.8 Hz,1H), 3.08 (dd, J = 15.7 Hz, J = 6.1 Hz, 1H), 3.71 (dd, J = 11.2 Hz, J = 5.3 Hz, 1H), 3.82 (ddd, J = 11.7 Hz, J = 9.2 Hz, J = 6.2 Hz, 1H), 3.95 (ddd, J = 6.1 Hz, J = 4.1 Hz, J = 1.3 Hz, 1H), 4.10 (d, J = 4.1 Hz, 1H), 6.86 (td, J = 6.8 Hz, J = 1.7 Hz,1H), 6.98 (ddd, J = 7.8 Hz, J = 7.8 Hz, J = 1.0 Hz, 1H), 7.04−7.14 (m, 5H), 7.26 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 11.14 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ = 21.2, 23.9, 24.9, 43.3, 57.5, 66.9, 85.1, 108.3, 111.7, 118.3, 118.8, 119.4 (2 carbons), 121.6 (2 carbons), 126.1, 128.6 (2 carbons), 134.3, 136.3, 155.0, 170.6 ppm; IR $\tilde{\nu}$ = 3164 (NH), 1610 (C═O), 1456; MS (ES) m/z (rel intens, %) = 360 (100) [M + H]$^+$; HRMS (ESI) calcd for $C_{22}H_{22}N_3O_2^+$ [M + H]$^+$ 360.1707, found 360.1700.

*(6R,13S,13aS)-13-(Phenylamino)-1,2,3,6,7,12,13,13a-octahydro-5H-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-b]indol-5-one (**14h**).* Following general procedure B using 3 equiv of aniline, **14h** was obtained as the insoluble residue from rinsing the crude with acetonitrile: yield 24% (43 mg); brown powder; mp 198−202 °C; $[\alpha]_D^{20}$ = +108.9 (c = 0.21 in THF); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.78−1.82 (m, 1H), 1.82−1.98 (m, 2H), 2.12−2.21 (m, 1H), 2.74−2.86 (m, 2H), 3.07 (dd, J = 15.5 Hz, J = 6.2 Hz, 1H), 3.51 (d, J = 3.8 Hz, 1H), 3.53 (dd, J = 11.2 Hz, J = 4.7 Hz, 1H), 3.78−3.88 (m, 2H), 5.51 (s, 1H), 6.44−6.56 (m, 1H), 6.86−6.92 (m, 4H), 6.94 (ddd, J = 7.6 Hz, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.00 (ddd, J = 7.6 Hz, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 10.63 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ = 21.2, 24.4, 24.6, 42.8, 56.0, 66.1, 67.2, 107.4, 111.6, 116.2 (2 carbons), 117.3, 117.9, 118.5, 120.9, 126.5, 127.9 (2 carbons), 135.8, 136.9, 145.8, 170.9 ppm; IR $\tilde{\nu}$ = 3195 (NH), 1601 (C═O), 1498, 1456; MS (ES) m/z (rel intens, %) = 359 (100) [M + H]$^+$, 717 (25); HRMS (ESI) calcd for $C_{22}H_{23}N_4O^+$ [M + H]$^+$ 359.1866, found 359.1877.

*(6R,13S,13aS)-13-(Benzyloxy)-1,2,3,6,7,12,13,13a-octahydro-5H-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-b]indol-5-one (**14i**).* Following general procedure B using 1.5 equiv of benzyl alcohol, **14i** was obtained via purification by pTLC as a white solid: yield 26% (49 mg); white solid; R_f = 0.41 (EtOAc); mp 134−138 °C; $[\alpha]_D^{20}$ = −20.9 (c = 0.42 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.67−1.86 (m, 2H), 1.96−2.12 (m, 2H), 2.37 (s, 1H), 2.95 (ddd, J = 12.2 Hz, J = 10.2 Hz, J = 4.7 Hz, 1H), 3.04 (dd, J = 15.9 Hz, J = 1.4 Hz, 1H), 3.23 (dd, J = 15.9 Hz, J = 6.5 Hz, 1H), 3.66 (dd, J = 11.7 Hz, J = 4.9 Hz, 1H), 3.99 (ddd, J = 12.2 Hz, J = 9.4 Hz, J = 6.1 Hz, 1H), 4.18 (dd, J = 6.1 Hz, J = 1.4 Hz, 1H), 4.45 (d, J = 12.5 Hz, 1H), 4.91 (d, J = 12.5 Hz, 1H), 7.14 (ddd, J = 7.6 Hz, J = 7.6 Hz, J = 1.1 Hz, 1H), 7.21 (ddd, J = 7.6 Hz, J = 7.6 Hz, J = 1.1 Hz, 1H), 7.29−7.38 (m, 6H), 7.52 (d, J = 7.6 Hz, 1H), 8.05 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.5, 24.4, 25.7, 43.6, 57.9, 65.4, 66.7, 83.8, 111.2, 111.4, 119.0, 120.0, 122.8, 126.9 (3 carbons), 127.5, 128.5 (2 carbons), 133.4, 136.1, 138.7, 171.3 ppm; IR $\tilde{\nu}$ = 3258 (NH), 1620 (C═O), 1454; MS (ES) m/z (rel intens, %) = 374 (100) [M + H]$^+$, 747 (25); HRMS (ESI) calcd for $C_{23}H_{24}N_3O_2^+$ [M + H]$^+$ 374,1863, found 374.1861.

*(6R,13R,13aS)-13-(Benzylamino)-1,2,3,6,7,12,13,13a-octahydro-5H-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-b]indol-5-one (**14j**).* Following general procedure B using 1.5 equiv of benzylamine, **14j** was obtained on purification by pTLC as a white powder: yield 28% (52 mg); white powder ; R_f = 0.37 (EtOAc + 5% MeOH); mp 142−148 °C; $[\alpha]_D^{20}$ = +0.4 (c = 0.40 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.58−1.72 (m, 1H), 1.72−1.85 (m, 1H), 1.85−2.21 (m, 4H), 2.92 (ddd, J = 12.2 Hz, J = 10.2 Hz, J = 4.6 Hz, 1H), 3.05 (dd, J = 16.1 Hz, J = 1.3 Hz, 1H), 3.17 (dd, J = 16.1 Hz, J = 6.5 Hz, 1H), 3.53 (dd, J = 11.8 Hz, J = 4.6 Hz, 1H), 3.62 (d, J = 13.5 Hz, 1H), 3.98 (d, J = 13.5 Hz, 1H), 3.95−4.03 (m, 1H), 4.19 (dd, J = 6.4 Hz, J = 1.3 Hz, 1H), 7.11 (ddd, J = 7.6 Hz, J = 7.6 Hz, J = 1.1 Hz, 1H), 7.19 (ddd, J = 7.6 Hz, J = 7.6 Hz, J = 1.1 Hz, 1H), 7.25−7.36 (m, 6H), 7.50 (d, J = 7.6 Hz, 1H), 8.32 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.5, 25.1, 25.2, 43.2, 46.2, 57.1, 67.2, 67.9, 110.1, 111.2, 118.7, 119.7, 122.5, 127.2, 127.3, 127.7 (2 carbons), 128.6 (2 carbons), 134.8, 135.7, 140.2, 170.9 ppm; IR $\tilde{\nu}$ = 3291 (NH), 1622 (C═O), 1456; MS (ES) m/z (rel intens, %) = 373 (100) [M + H]$^+$; HRMS (ESI) calcd for $C_{23}H_{25}N_4O^+$ [M + H]$^+$ 373,2023, found 373.2019.

Procedure for the Synthesis of (6*R*,13*R*,13a*S*)-13-Butyl-1,2,3,6,7,12,13,13a-octahydro-5*H*-6,13-epiminopyrrolo[1′,2′:1,2]azocino[4,5-*b*]indol-5-one (14k). A solution of α-chloroamine **12** (1 equiv, 0.5 mmol, 151 mg) in dry THF (10 mL) was cooled to −78 °C. Butyllithium (3 equiv, 1.5 mmol, 0.8 mL of 2 M BuLi in hexanes) was added, and the mixture was allowed to warm to room temperature. After 30 min the mixture was quenched by the careful addition of water (10 mL). Ethyl acetate (15 mL) was added subsequently, and the layers were separated. The aqueous layer was extracted with ethyl acetate (10 mL). The combined organic phases were washed three times with water (10 mL) and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure yielded a yellow powder. Purification by pTLC using ethyl acetate as the eluent gave compound **14k** as a white powder: yield 12% (19 mg); white powder; R_f = 0.37 (EtOAc + 5% MeOH); mp 204−206 °C; $[\alpha]_D^{20}$ = −29.6 (c = 0.27 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.85 (t, J = 7.1 Hz, 3H), 1.05−1.17 (m, 1H), 1.24−1.38 (m, 3H), 1.58−2.04 (m, 7H), 2.87 (ddd, J = 12.1 Hz, J = 9.8 Hz, J = 4.4 Hz, 1H), 3.03 (dd, J = 16.1 Hz, J = 1.7 Hz, 1H), 3.09 (dd, J = 16.1 Hz, J = 6.0 Hz, 1H), 3.33 (dd, J = 11.6 Hz, J = 4.5 Hz, 1H), 3.98 (ddd, J = 12.1 Hz, J = 9.5 Hz, J = 6.0 Hz, 1H), 4.10 (dd, J = 6.0 Hz, J = 1.7 Hz, 1H), 7.09 (ddd, J = 7.7 Hz, J = 7.7 Hz, J = 1.1 Hz, 1H), 7.15 (ddd, J = 7.7 Hz, J = 7.7 Hz, J = 1.1 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 8.26 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 21.7, 23.3, 25.7, 25.8, 26.0, 35.0, 43.0, 53.1, 55.0, 67.9, 108.5, 111.1, 118.6, 119.8, 122.1, 127.3, 136.0, 136.9, 171.2 ppm; IR $\tilde{\nu}$ = 3254 (NH), 1614 (C═O), 1455; MS (ES) m/z (rel intens, %) = 324 (100) [M + H]$^+$; HRMS (ESI) calcd for $C_{20}H_{26}N_3O^+$ [M + H]$^+$ 324,2070, found 324.2082.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01161.

X-ray data for **12d** (CIF)

Data regarding the theoretical calculations and ^{1}H and ^{13}C NMR spectra of all characterized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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