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Synthesis of Chiral Piperazinones Using Amphoteric Aziridine Aldehyde Dimers and Functionalized Isocyanides

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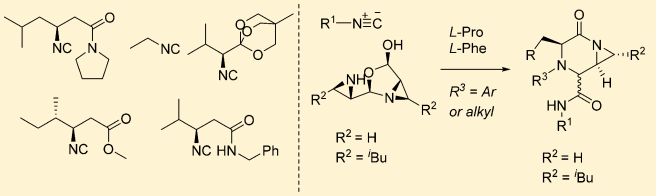
Supporting Information

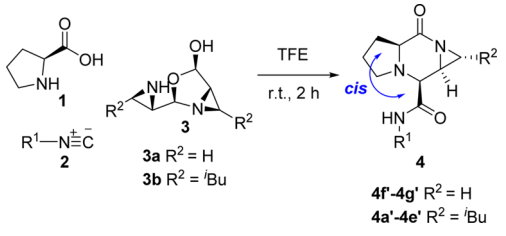
ABSTRACT: We have evaluated a range of functionalized isocyanides in the aziridine aldehyde-driven multicomponent synthesis of piperazinones. High diasteroselectivity for each isocyanide was observed. A theoretical evaluation of the reaction course corroborates the experimental data. Moreover, the reactivity of *cis*- and *trans*-configured aziridine aldehyde dimers has been compared. This study further probes the dimer-driven mechanism of cyclization and enables an efficient access to a wide range of chiral piperazinones bearing functionalized side chains.



Due to their diverse biological activity, chiral piperazinones continue to serve as important targets of chemical synthesis.[1] However, the construction of functionally rich piperazinones still requires a number of protecting group manipulations.[2] Multicomponent reactions (MCR) have been utilized to address this challenge.[3] MCRs facilitate synthesis by offering a convergent approach, which significantly increases the molecular complexity.[4] Nonetheless, efficient control of stereochemistry remains challenging.[5] Previously, we have reported the development of an MCR-driven construction of piperazinones from amphoteric aziridine aldehyde dimers. This reaction allowed for the rapid access to piperazinones with high stereoselectivity (Scheme 1).[6] In this process, the homochiral aziridine aldehyde dimer participates in iminium ion formation with an amino acid, followed by stereoselectivity-determining isocyanide addition.[7] Finally, the aziridine attacks the carbonyl group of the mixed anhydride, directing the reaction toward piperazinone formation.[8]

In the present study, we have evaluated a diverse range of functionalized isocyanides (Figure 1) in the aziridine aldehyde-driven MCR. One of the goals was to investigate the isocyanide's influence on diastereoselectivity. Additionally, we sought to examine the effect of aziridine aldehyde dimer on the diastereoselectivity of piperazinone synthesis. This study has significantly increased the scope of the reaction, offering uniquely functionalized piperazinones that are capable of undergoing downstream functionalization. A computational evaluation of the role of the isocyanide backbone on stereoselectivity has been carried out, and the results were compared to experimental data.

Scheme 1. Three-Component MCR with L-Proline 1, Isocyanide 2 and Aziridine Aldehyde Dimer 3 to Afford Chiral Piperazinone 4



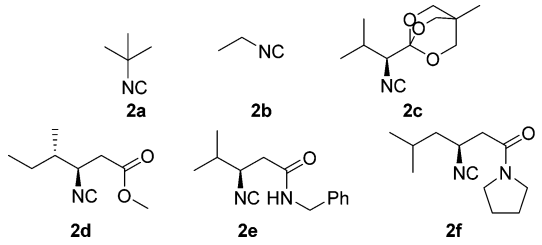


Figure 1. Isocyanides utilized in aziridine-aldehyde driven MCR.

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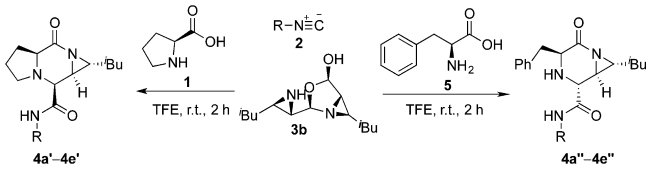
Initially, we screened different isocyanides **2b**−**2f** with bulky isobutyl aziridine aldehyde dimer (**3b**) and L-proline (**1**) or L-phenylalanine (**5**) to yield a wide range of functionally diverse piperazinones (Table 1). The target molecules were synthesized in good to excellent yields−up to 87% from ethyl isocyanide (**2b**). In the presence of L-proline, the "matched-case" iminium-ion attack, in which the isocyanide backbone interacts with the carboxylate group, preferentially affords the *cis*-product (entries 1−5). The bulky orthoester backbone of **2c** increases the stereoselectivity up to 84/16 (*cis*/*trans* ratio). On the other hand, electron-withdrawing groups on the isocyanide, such as amides or esters **2d**−**2f** decrease the diastereoselectivity, resulting in diminished *cis*-product formation. Despite the relatively sterically unhindered ethyl portion of the isocyanide reagent **2b**, high stereoselectivity was still observed in this case.

Table 1. Reaction Scope with *trans*-Aziridine Aldehyde Dimer 3b[a]



entry	amino acid	isocyanide	product	selectivity, crude (%) *cis*	selectivity, crude (%) *trans*	yield (%)[b]
1	L-Pro	**2b**	**4a′**	78	22	87
2	L-Pro	**2c**	**4b′**	84	16	72
3	L-Pro	**2d**	**4c′**	72	28	60
4	L-Pro	**2e**	**4d′**	77	23	71
5	L-Pro	**2f**	**4e′**	70	30	52
6	L-Phe	**2b**	**4a″**	15	85	55[c]
7	L-Phe	**2c**	**4b″**	19	81	60
8	L-Phe	**2d**	**4c″**	30	70	77
9	L-Phe	**2f**	**4e″**	14	86	46

[a]Selectivity was assigned by ^{1}H NMR of crude reaction mixture. [b]Isolated yield. [c]Pure *trans*-product isolated.

NOE interactions of H_a with H_b as well as H_c were observed for **4a′**−**4f′** using L-proline. These cross peaks of the main diastereomer confirmed the *cis*-product formation. The *cis*/*trans* stereochemistry is defined by the relative stereochemistry between the subtituents on carbons 2 and 4 in the piperazinone ring (Figure 2). In the presence of the primary amino acid L-phenylalanine, the *trans*-diastereomer was observed predominantly (entries 6−9). In this case, NOE cross peaks of H_d with H_e as well as H_f with H_g were detected (Figure 2). Ethyl isocyanide (**2b**) and the orthoester **2c** favored *trans*-product formation using L-phenylalanine (entries 6−7), whereas the ester **2d** led clearly to an erosion of the stereoselectivity (entry 8). Presumably, an interaction of the isobutyl group of aziridine aldehyde dimer **3b** with the ester backbone decreases the selectivity for the *trans*-product formation. However, in the presence of the sterically demanding amide group on the isocyanide, high stereoselectivity was observed for **2f** (entry 9). It appears that not only the electronic structure but also steric effects are influencing the diastereoselectivity.

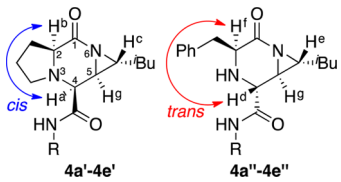
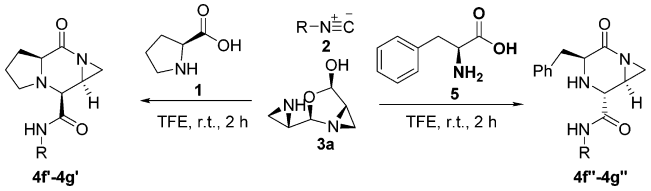


Figure 2. Stereochemical assignment by 1D-NOESY NMR of *cis*-piperazinones **4a′**−**4e′** and *trans*-piperazinones **4a″**−**4e″**.

Next, we used unsubstituted aziridine aldehyde dimer **3a** with isocyanides **2b** and **2d** to study the influence of aziridine aldehyde sterics on the stereoselective outcome of the reaction in greater detail (Table 2). Higher selectivity and better isolated yields were obtained in these experiments again with ethyl isocyanide (**2b**). In general, the same selectivity trends were observed with the aziridine aldehyde dimer **3a** compared to **3b**. However, the diastereoselectivity of reactions with **3a** was higher than those with **3b**. This suggests that the dimer sterics does not strongly influence the stereoselectivity of the reaction.

Table 2. Disrupted Ugi Reaction with 3a



entry	amino acid	isocyanide	product	selectivity, crude (%) *cis*	selectivity, crude (%) *trans*	yield (%)[a]
1	L-Pro	**2b**	**4f′**	90	10	75
2	L-Pro	**2d**	**4g′**	84	16	39
3	L-Phe	**2b**	**4f″**	13	87	48
4	L-Phe	**2d**	**4g″**	16	84	33

[a]Isolated yield.

Previous computational analysis of this MCR with aziridine aldehydes revealed that selectivity was set during isocyanide addition.[8] Four possible addition modes, arising from attack of isocyanide on the *re* or *si* face of the E or Z imine (***Z*-pro(*S*)**, ***Z*-pro(*R*)**, ***E*-pro(*S*)**, and ***E*-pro(*R*)**), gave rise to two possible stereoisomers. Transition state analysis revealed that isocyanide preferentially attacks from the same face as the carboxylate, as a result of stabilizing interactions between the carboxylate and the incoming isocyanide. As a consequence, ***Z*-pro(*S*)** and ***E*-pro(*R*)** are the two lowest energy transition states for each facial addition. A combination of favorable secondary features of ***Z*-pro(*S*)**, and a thermodynamic preference for the *Z*-iminium ion result in preferential formation of the (*S*)- isomer, consistent with experimental results.

Accordingly, using the established model, DFT calculations at the MPWPW91/6-31G(d) (IEFPCM = 2,2,2-trifluoroethanol) level confirm the experimentally observed preferential formation of the *cis*-products, shedding insight into the reaction in question and further validating the existing model. Four transition states, corresponding to the four addition modes (**Z-pro(*S*)**, **Z-pro(*R*)**, **E-pro(*S*)**, and **E-pro(*R*)**), were modeled with ethyl isocyanide. The inclusion of TFE was assisted by a conformational search using Macro-model, implementing the OPLS Force field, a constant dielectric of 1.0, and the TNCG minimization algorithm. The molecule containing the iminium ion was constrained, as were the C,N,C atoms of the isocyanide. A mixed torsional/low-mode sampling conformational search was performed using 100 steps per rotatable bond

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and 5 kcal/mol energy cutoff. The lowest energy conformation was then used as the template for further DFT optimized transition states. In each case, the preferred location for TFE was coordinated to the carboxylate ion.

Consistent with the experimental observations, computations revealed a 1.88 kcal/mol energetic preference for the pro(S) transition state, relative to the lowest pro(*R*) transition state. Notably, the lowest pro(*R*) and pro(*S*) transition states correspond to *cis*-addition modes (relative to the carboxylate), reaffirming carboxylate facilitated transition state stabilization (Figure 3).

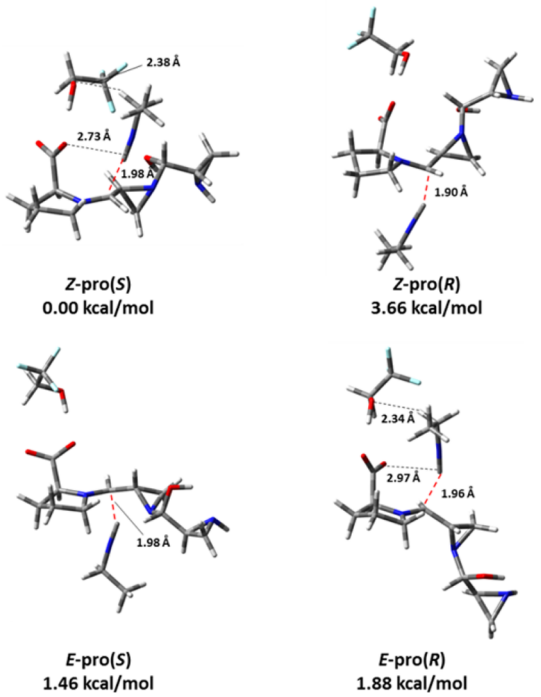
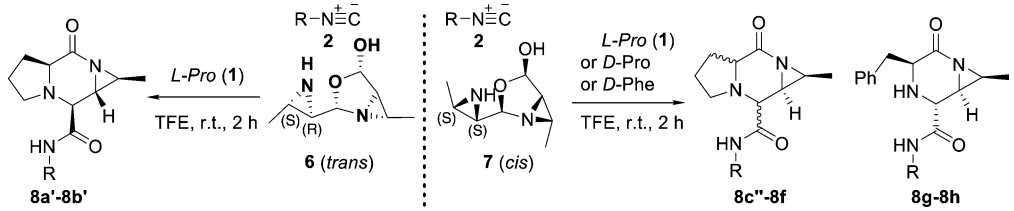


Figure 3. MPWP91/6-31G(d)-computed isocyanide addition in the transition state favors the *cis*-product formation in accordance to experimental results.

Furthermore, it appears that the amphiphilic nature of isocyanide is important for both reactivity and selectivity. The transition state is stabilized by donation from the aziridine ring into the incipient C−C bond, in addition to donation from the incoming nucleophile into the aziridine ring (*vide infra*). The lowest energy pro-(*R*) transition state, **E-pro(*R*)**, is a *cis*-addition mode, with a Bürgi-Dunitz attack trajectory of 107.3°. With the inclusion of an explicit solvent molecule, no stabilizing interaction between the carboxylate oxygen and the C−N bond of isocyanide was detected by NBO analysis. Nevertheless, NBO analysis did support the presence of a stabilizing Coulombic interaction between the carboxylate-coordinated TFE solvent molecule and the CH groups of the incoming isocyanide (E_{NBO} = 3.59 kcal/mol, O−C interatomic distance = 2.38 Å). In addition to indirect carboxylate stabilization, NBO analysis revealed a 4.36 kcal/mol stabilization energy from donation of the antiperiplanar C−N bond of the aziridine into the forming C−C bond and a 4.72 kcal/mol donation from the C−C bond into the antiperiplanar aziridine C−N bond. The lowest pro(*S*) transition state, **Z-pro(*S*)**, also conforms to a *cis*-addition mode, though the attack trajectory of the incoming isocyanide deviates slightly from an ideal Bürgi-Dunitz angle (111.1°). The **Z-pro(*S*)** geometry possess a much shorter distance between the carboxylate oxygen and the isocyanide carbon atom involved in bond formation (2.73 Å), which according to NBO analysis is accompanied by significant stabilization (E_{NBO} = 1.45 kcal/mol). Furthermore, the carboxylate-coordinated TFE solvent molecule was found to stabilize the transition state through cooperative hydrogen bonding interaction between a hydrogen of the isocyanide the TFE solvent molecule and the carboxylate (E_{NBO} = 2.18 kcal/mol). In addition to carboxylate stabilization, NBO analysis revealed stabilization associated with donation of the antiperiplanar C−C bond of the aziridine into the forming C−C bond (E_{NBO} = 5.45 kcal/mol), and donation of this incipient C−C bond into the C−C bond of the aziridine ring (E_{NBO} = 3.81 kcal/mol).

We then compared the reactivity and stereoselectivity of diastereomeric *cis*- and *trans*-aziridine aldehyde dimers (Table

Table 3. Methyl Aziridine Aldehyde Driven Three Component Reactions with Diverse Isocyanides



entry	amino acid	dimer	isocyanide	product	selectivity, crude (%) *cis*	selectivity, crude (%) *trans*	yield (%)[a]
1	L-Pro	*trans*	**2a**	**8a′**	63	37	37
2	L-Pro	*trans*	**2b**	**8b′**	>95	<5	21
3	D-Pro	*cis*	**2a**	**8c″**	>95	<5	53
4	L-Pro	*cis*	**2b**	**8d′**	>95	<5	74
5	D-Pro	*cis*	**2b**	**8d″**	87	13	58
6	D-Pro	*cis*	**2c**	**8e″**	>95	<5	43
7	D-Pro	*cis*	**2e**	**8f**	>95	<5	42
8	D-Phe	*cis*	**2c**	**8g**	5	95	33
9	D-Phe	*cis*	**2d**	**8h**	26	74	41

[a]Isolated yield.

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3). Using *trans*-aziridine aldehyde dimer **6**, a moderate yield (up to 37%, entries 1−2) was observed. Interestingly, a high stereoselectivity was only observed when using ethyl isocyanide (**2b**) and L-proline (**1**) as reaction partners. This result demonstrates the importance of the isocyanide backbone for the reaction with *trans*-aziridine-aldehyde dimer. In the presence of the *cis* aziridine aldehyde dimer **7**, excellent diastereoselectivities and moderate to good yields were obtained (entries 3−7). Additional methyl groups of dimer **7** are most likely preventing the isocyanide attack via the ***Z*-pro(*R*)** transition state due to sterical hindrance. Although we varied the configuration of the amino acid, the *cis*-product was observed in all cases almost exclusively. Using the primary amino acid D-phenylalanine led to a slight decrease of both yields and diastereoselectivities (entries 8−9). However, the electron rich isocyanide **2c** increased the diastereoselectivity of the reaction drastically to receive mainly the *trans*-product **8g**.

In conclusion, we have expanded the scope of the aziridine aldehyde driven MCR by using diverse isocyanides, including the unique ethyl isocyanide (**2b**) to obtain chiral piperazinones in high stereoselectivities. These results are in accordance with our MPWP91/6-31G(d)-computations for L-proline, which verified interactions of the carboxylate group of **Z-5** with the ethyl portion of isocyanide **2b** to favor the *cis*-product formation. This interaction is also the main factor in diastereoselectivity. In the presence of *cis*-methyl aziridine-aldehyde dimer **7**, proline and diverse isocyanides, the *cis*-diastereomer was received almost exclusively, even if the stereochemistry of the amino acid was inverted. In future work, the biological activity of these medicinally relevant piperazinones will be probed. Furthermore, we can now utilize functionalized isocyanides in the aziridine aldehyde-driven macrocyclization reaction of peptides, and the isocyanide derived handle will be utilized in downstream functionalization of the macrocyclic peptides.

EXPERIMENTAL SECTION

Computational Methods. Calculations were carried out at the MPWPW91/6-31G (d)level of theory using Gaussian 09 and GaussView v5.0.8. programs. All transition states were confirmed by the presence of a single imaginary frequency and all minima were confirmed to be local minima by the presence of only real irrational frequencies. NBO calculations were performed using Gaussian NBO version 3.1.

General Methods. All reactions containing moisture- or air-sensitive reagents or intermediates were carried out under nitrogen atmosphere in oven-dried glassware using standard Schlenk techniques. Thin layer chromatography (TLC) was performed on precoated glass backed TLC plates using UV light (254 nm) or $KMnO_4$ solution for detection. Flash chromatography (FC) was carried out on Silicycle 230−400 mesh silica gel with a nitrogen overpressure up to 0.5 bar.. 2,2,2-Trifluoroethanol, ethyl acetate, methanol, hexanes and *tert*-butylisocyanide were used as received.

^1H and ^{13}C NMR spectra were recorded at 300 K on 400 or 500 MHz spectrometers. The chemical shifts δ were reported in parts per million (ppm) and referred to the solvent ($CDCl_3$) residual peak (^1H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm). Multiplicity of the signals: s (singlet), d (doublet), t (triplet), bs (broad signal), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), qd (quartet of doublets), ddd (doublets of doublets of doublets) and m (multiplet). The coupling constants are reported in Hertz (Hz). Melting points (MP) were and are uncorrected. Mass spectroscopy (MS) was carried out using DART in positive ion mode.

General Procedure for the Ugi-Reaction to Afford Chiral Piperazinones (GP1). To a screw-capped vial equipped with a magnetic stirring bar was added the amino acid (100 μmol) in 0.5 mL TFE. Aziridine aldehyde dimer (50.0 μmol) and isocyanide (100 μmol) were added and the mixture was stirred for 2 h. The solvent was removed under a stream of nitrogen and the crude material was purified via FC to afford the product.

Synthesis of Chiral Piperazinones. *(1R,3aS,8S,8aS)-N-Ethyl-1-isobutyl-3-oxohexahydro-1H,3H-azirino[1,2-a]pyrrolo[1,2-d]-pyrazine-8-carboxamide (**4a**′).* According to **GP1** with (2*R*,4*R*,5*S*,6*R*)-6-isobutyl-2-((2*S*,3*R*)-3-isobutylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (**3b**) (50.0 μmol), L-proline (100 μmol) and ethyl isocyanide (2b) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 78/22) **4a**′(24 mg, 87 μmol, 87%) as a colorless solid, with minor amounts of (1*R*,3a*S*,8*R*,8a*S*)-*N*-ethyl-1-isobutyl-3-oxohexahydro-1*H*,3*H*-azirino[1,2-*a*]pyrrolo[1,2-*d*]pyrazine-8-carboxamide.

Main diastereomer: ^1H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.93 (dd, *J* = 9.2, 6.7 Hz, 6H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.18−1.26(m, 1H), 1.57−1.64 (m, 1H), 1.67−1.77 (m, 1H), 1.78−1.92 (m, 3H), 2.04−2.28 (m, 2H),2.43−2.48 (m, 1H), 2.80 (dd, *J* = 6.2, 3.7 Hz, 1H), 2.89−2.94 (m, 1H), 3.09−3.14 (m, 1H), 3.28−3.44 (m, 2H), 3.49 (d, *J* = 6.2 Hz, 1H), 6.41 (bs, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 15.1, 21.8, 22.1, 22.4, 22.6, 26.8, 34.1, 41.6, 42.3, 43.7, 54.6, 63.0, 64.5, 169.5, 183.1 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{15}H_{26}N_3O_2$ ($[M + H]^+$) 280.2025, found 280.2030; mp (mixture of diastereomers,$CDCl_3$) Decomposition 184 °C.

*(1R,3aS,8S,8aS)-1-Isobutyl-N-((S)-2-methyl-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propyl)-3-oxohexahydro-1H,3H-azirino[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxamide (**4b**′).* According to **GP1** with (2*R*,4*R*,5*S*,6*R*)-6-isobutyl-2-((2*S*,3*R*)-3-isobutylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (**3b**) (50.0 μmol), L-proline (100 μmol) and (*S*)-1-(1-isocyano-2-methylpropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**2c**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 82/18) **4b**′ (31 mg, 72 μmol, 72%) as a yellow solid with minor amounts of (1*R*,3a*S*,8*R*,8a*S*)-1-isobutyl-*N*-((*S*)-2-methyl-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)propyl)-3-oxohexahydro-1*H*,3*H*-azirino[1,2-*a*]pyrrolo[1,2-*d*]pyrazine-8-carboxamide.

Main diastereomer: ^1H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.76−1.01 (m, 15 H), 1.13−1.21 (m, 1H), 1.30−1.52 (m, 2H), 1.70−1.93 (m, 4H),2.07−2.26 (m, 2H), 2.50−2.56 (m, 1H), 2.81 (dd, *J* = 6.8, 3.7 Hz, 1H), 2.87−2.91 (m, 1H), 3.28−3.33 (m, 1H), 3.50 (d, *J* = 6.1 Hz, 1H), 3.82−3.86 (m,6H), 4.06 (dd, *J* = 10.3, 3.2 Hz, 1H), 6.61 (d, *J* = 10.3 Hz, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 14.3, 17.1, 21.1, 21.8, 21.9, 22.9, 23.0, 26.7, 27.5, 30.5, 41.2, 42.5, 43.1, 53.9, 56.2, 62.7, 64.5, 3 × 72.5, 108.4, 169.9, 183.0 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{23}H_{38}N_3O_5$ ($[M + H]^+$) 436.2812, found 436.2799; mp (mixture of diastereomers, $CDCl_3$) 112 °C.

*Methyl (3R,4S)-3-((1R,3aS,8S,8aS)-1-isobutyl-3-oxohexahydro-1H,3H-azirino[1,2-a]pyrrolo-[1,2-d]pyrazine-8-carboxamido)-4-methylhexanoate (**4c**′).* According to **GP1** with (2*R*,4*R*,5*S*,6*R*)-6-isobutyl-2-((2*S*,3*R*)-3-isobutylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]-hexan-4-ol (**3b**) (50.0 μmol), L-proline (100 μmol) and methyl (3*R*,4*S*)-3-isocyano-4-methylhexanoate (**2d**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 71/29) **4c**′ (24 mg, 60 μmol, 60%) as a colorless solid with minor amounts of methyl (3*R*,4*S*)-3-((1*R*,3a*S*,8*R*,8a*S*)-1-isobutyl-3-oxohexahydro-1*H*,3*H*-azirino[1,2-*a*]pyrrolo[1,2-*d*]pyrazine-8-carboxamido)-4-methylhexanoate.

Main diastereomer: ^1H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.86−1.01 (m, 12 H), 1.03−1.17 (m, 1H), 1.23−1.30 (m, 1H), 1.35−1.51 (m, 2H),1.55−1.69 (m, 1H), 1.74−1.91 (m, 4H), 2.06−2.23 (m, 2H), 2.40−2.53 (m, 3H), 2.54−2.64 (m, 1H), 2.81 (dd, *J* = 6.2, 3.7 Hz, 1H), 2.87−2.92 (m,1H), 3.14−3.22 (m, 1H), 3.48 (d, *J* = 6.2 Hz, 1H), 3.66 (s, 3H), 6.85 (d, *J* = 9.2 Hz, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 11.2, 15.2, 21.6, 21.8, 22.0, 22.9, 25.8, 26.8, 35.8, 37.6, 41.3, 42.2, 43.1, 50.0, 51.8, 54.4, 62.9, 64.3, 169.2, 172.2, 182.8 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{21}H_{36}N_3O_4$

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([M + H]$^+$) 394.2706, found 394.2715; mp (mixture of diastereomers, $CDCl_3$) 97 °C.

*(1R,3aS,8S,8aS)-N-((R)-1-(Benzylamino)-4-methyl-1-oxopentan-3-yl)-1-isobutyl-3-oxohexahydro-1H,3H-azirino[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxamide (**4d′**).* According to **GP1** with (2*R*,4*R*,5*S*,6*R*)-6-isobutyl-2-((2*S*,3*R*)-3-isobutylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (3b) (50.0 μmol), L-proline (100 μmol) and (*R*)-*N*-benzyl-3-isocyano-4-methylpentanamide (2e) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 77/23) **4d′** (32 mg, 71 μmol, 71%) as a colorless solid with minor amounts of (1*R*,3a*S*,8*R*,8a*S*)-*N*-((*R*)-1-(benzylamino)-4-methyl-1-oxopentan-3-yl)-1-isobutyl-3-oxohexahydro-1*H*,3*H*-azirino[1,2-*a*]pyrrolo[1,2-*d*]-pyrazine-8-carboxamide.

Main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.87−0.96 (m, 12 H), 1.18−1.25 (m, 2H), 1.28−1.41 (m, 1H), 1.67−1.97 (m, 6H),2.02−2.16 (m, 1H), 2.35−2.51 (m, 3H), 2.73 (dd, *J* = 6.1, 3.7 Hz, 1H), 2.80 (dd, *J* = 8.8, 7.7 Hz,1H), 3.09−3.15 (m, 1H), 3.37 (d, *J* = 6.1 Hz, 1H), 3.97−4.03 (m, 1H), 4.36 (d, *J* = 5.9 Hz, 2H), 6.45 (t, *J* = 5.6 Hz, 1H), 7.16−7.32 (m, 5H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 19.3, 19.5, 21.7, 22.0, 22.0, 23.0, 26.8, 31.5, 38.0, 41.4, 42.2, 43.3, 43.6, 51.9, 54.4, 63.1, 64.6, 127.6, 2 × 127.9, 2 × 128.8, 138.2, 169.6, 170.7, 182.9 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{26}H_{39}N_4O_3$ ([M + H]$^+$) 455.3021, found 455.3022; mp (mixture of diastereomers, $CDCl_3$) 148−152 °C.

*(1R,3aS,8S,8aS)-1-Isobutyl-N-((S)-5-methyl-1-oxo-1-(pyrrolidin-1-yl)hexan-3-yl)-3-oxohexahydro-1H,3H-azirino[1,2-a]pyrrolo[1,2-d]-pyrazine-8-carboxamide (**4e′**).* According to **GP1** with (2*R*,4*R*,5*S*,6*R*)-6-isobutyl-2-((2*S*,3*R*)-3-isobutylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (**3b**) (50.0 μmol), L-proline (100 μmol) and (*S*)-3-isocyano-5-methyl-1-(pyrrolidin-1-yl)hexan-1-one (**2f**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 69/31) **4e′** (22 mg, 52 μmol, 52%) as a colorless solid with minor amounts of (1*R*,3a*S*,8*R*,8a*S*)-1-isobutyl-*N*-((*S*)-5-methyl-1-oxo-1-(pyrrolidin-1-yl)-hexan-3-yl)-3-oxohexahydro-1*H*,3*H*-azirino[1,2-*a*]pyrrolo[1,2-*d*]-pyrazine-8-carboxamide.

Main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.85−0.91 (m, 9H), 0.92−0.95 (m, 4H), 1.15−1.37 (m, 3H), 1.43−1.54 (m, 1H),1.59−1.87 (m, 7H), 1.88−1.95 (m, 2H), 2.04−2.10 (m, 1H), 2.41−2.55 (m,3H), 2.73 (dd, *J* = 6.0, 3.7 Hz, 1H), 2.78−2.81 (m, 1H), 3.14−3.19 (m, 1H), 3.32−3.43 (m, 5H), 4.24−4.33 (m, 1H), 7.40 (d, *J* = 9.3 Hz, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 21.7, 22.0, 22.1, 22.2, 23.0, 23.2, 24.4, 25.2, 26.1, 26.9, 38.9, 41.5, 42.1, 43.1, 43.4, 43.9, 45.6, 46.8, 54.4, 63.1, 64.5, 169.2, 169.4, 182.9 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{24}H_{41}N_4O_3$ ([M + H]$^+$) 433.3179, found 433.3180; mp (mixture of diastereomers, $CDCl_3$) 108 °C.

*(3S,5R,6R,7R)-3-Benzyl-N-ethyl-7-isobutyl-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamide (**4a″**).* According to **GP1** with (2*R*,4*R*,5*S*,6*R*)-6-isobutyl-2-((2*S*,3*R*)-3-isobutylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (**3b**) (50.0 μmol), L-phenylalanine (100 μmol) and ethyl isocyanide (**2b**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired *trans*-product **4a″** (18 mg, 55 μmol, 55%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.74 (t, *J* = 7.3 Hz, 3H), 1.00 (dd, *J* = 6.7, 5.0 Hz, 6H), 1.41−1.55(m, 2H), 1.78 (bs, 1H), 1.83−1.92 (m, 1H), 2.24 (ddd, *J* = 7.1, 5.5, 3.7 Hz, 1H), 2.53 (dd, *J* = 14.4, 11.0 Hz, 1H), 2.81−2.90 (m, 1H), 2.95−3.08 (m, 2H), 3.18−3.24 (m, 2H), 3.56 (bs, 1H),6.60 (s, 1H), 7.21−7.37 (m, 5H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 14.5, 22.4, 22.8, 27.1, 34.1, 35.1, 41.1, 41.4, 43.3, 53.7, 57.8, 126.9, 2 × 128.6, 2 × 129.5, 138.5, 169.8, 185.0 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{19}H_{28}N_3O_2$ ([M + H]$^+$) 330.2182, found 330.2181; mp ($CDCl_3$) 158−162 °C.

*(3S,5R,6R,7R)-3-Benzyl-7-isobutyl-N-((S)-2-methyl-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)propyl)-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamide (**4b″**).* According to **GP1** with (2*R*,4*R*,5*S*,6*R*)-6-isobutyl-2-((2*S*,3*R*)-3-isobutylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (**3b**) (50.0 μmol), L-phenylalanine (100 μmol) and (*S*)-1-(1-isocyano-2-methylpropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**2c**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 17/83) **4b″** (29 mg, 60 μmol, 60%) as a yellow solid with minor amounts of (3*S*,5*S*,6*R*,7*R*)-3-benzyl-7-isobutyl-*N*-((*S*)-2-methyl-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propyl)-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamide.

Main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.69 (s, 3H), 0.70−1.01 (m, 12H), 1.38−1.53 (m, 1H), 1.80−1.91 (m, 1H),1.94 (bs, 1H), 2.11−2.21 (m, 2H), 2.87 (dd, *J* = 14.7, 5.4 Hz, 1H), 3.15 (dd, *J* = 14.3, 7.6 Hz, 1H), 3.26 (dd, *J* = 3.6, 2.3 Hz, 1H), 3.38−3.44 (m,1H), 3.51−3.54 (m, 1H), 3.69−3.77 (m, 6H), 3.89−3.96 (m, 1H), 4.05 (dd, *J* = 10.7, 3.5 Hz, 1H), 7.15−7.31 (m, 5H), 7.47 (d, *J* = 10.6 Hz, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 14.4, 17.1, 21.2, 22.4, 22.8, 27.0, 27.7, 30.6, 35.3, 41.1, 42.6, 43.5, 54.1, 56.2, 56.7, 3 × 72.5, 108.6, 126.6, 2 × 128.5, 2 × 129.5, 137.8, 170.5, 185.5 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{27}H_{40}N_3O_5$ ([M + H]$^+$) 486.2968, found 486.2970; mp (mixture of diastereomers, $CDCl_3$) 78−85 °C.

*Methyl (3R,4S)-3-((3S,5R,6R,7R)-3-benzyl-7-isobutyl-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamido)-4-methylhexanoate (**4c″**).* According to **GP1** with (2*R*,4*R*,5*S*,6*R*)-6-isobutyl-2-((2*S*,3*R*)-3-isobutylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (**3b**) (50.0 μmol), L-phenylalanine (100 μmol) and methyl (3*R*,4*S*)-3-isocyano-4-methylhexanoate (**2d**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 31/69) **4c″** (34 mg, 77 μmol, 77%) as a yellow oil with minor amounts of methyl (3*R*,4*S*)-3-((3*S*,5*S*,6*R*,7*R*)-3-benzyl-7-isobutyl-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamido)-4-methylhexanoate.

Main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.69 (d, *J* = 6.9 Hz, 3H), 0.79−0.83 (m, 4H), 0.96−1.01 (m, 6H), 1.15−1.22 (m, 2H), 1.39−1.46 (m, 1H),1.47−1.51 (m, 1H), 1.67 (dd, *J* = 14.6, 9.8 Hz, 1H), 1.81−1.90 (m, 2H), 2.20−2.25 (m, 2H), 2.58 (dd, *J* = 14.1, 9.9 Hz, 1H), 3.17−3.19 (m, 1H), 3.20−3.27 (m, 2H), 3.56 (s, 1H), 3.61 (s, 3H), 4.03−4.09 (m,1H), 6.90 (d, *J* = 10.1 Hz, 1H), 7.15−7.32 (m, 5H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 11.4, 15.3, 22.4, 22.8, 25.2, 27.0, 35.4, 36.5, 38.6, 41.1, 41.8, 43.2, 50.2, 51.9, 53.4, 56.7, 126.7, 2 × 128.6, 2 × 129.9, 138.4, 169.8, 172.0, 185.3 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{25}H_{38}N_3O_4$ ([M + H]$^+$) 444.2862, found 444.2875.

*(3S,5R,6R,7R)-3-Benzyl-7-isobutyl-N-((S)-5-methyl-1-oxo-1-(pyrrolidin-1-yl)hexan-3-yl)-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamide (**4e″**).* According to **GP1** with (2*R*,4*R*,5*S*,6*R*)-6-isobutyl-2-((2*S*,3*R*)-3-isobutylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (**3b**) (50.0 μmol), L-phenylalanine (100 μmol) and (*S*)-3-isocyano-5-methyl-1-(pyrrolidin-1-yl)hexan-1-one (**2f**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 18/82) **4e″** (26 mg, 46 μmol, 46%) as a colorless solid with minor amounts of (3*S*,5*S*,6*R*,7*R*)-3-benzyl-7-isobutyl-*N*-((*S*)-5-methyl-1-oxo-1-(pyrrolidin-1-yl)hexan-3-yl)-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamide.

Main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.84 (dd, *J* = 6.6, 2.8 Hz, 6H), 0.98 (dd, *J* = 6.7, 3.5 Hz, 6H), 1.15−1.22 (m, 2H), 1.37−1.50 (m, 3H),1.77−1.89 (m, 3H), 1.89−2.00 (m, 3H), 2.15−2.24 (m, 3H), 2.70 (dd, *J* = 14.0, 8.3 Hz, 1H), 3.11−3.16 (m, 2H), 3.29 (bs, 1H), 3.34−3.44 (m, 4H), 3.46 (s, 1H), 4.12−4.21 (m, 1H), 7.19−7.33 (m, 5H), 7.39 (d, *J* = 9.2 Hz, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 21.8, 22.3, 22.7, 23.1, 24.3, 25.0, 26.1, 26.9, 35.2, 39.8, 40.9, 42.0, 2 × 43.1, 44.2, 45.6, 46.7, 53.8, 57.0, 126.5, 2 × 128.3, 2 × 129.8, 138.4, 169.0, 169.7, 185.4 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{28}H_{43}N_4O_3$ ([M + H]$^+$) 483.3335, found 483.3343; mp (mixture of diastereomers, $CDCl_3$) 67−70 °C.

*(3aR,8R,8aS)-N-Ethyl-3-oxohexahydro-1H,3H-azirino[1,2-a]-pyrrolo[1,2-d]pyrazine-8-carboxamide (**4f′**).* According to **GP1** with (2*R*,4*R*,5*S*)-2-((*S*)-aziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (**3a**) (50.0 μmol), L-proline (100 μmol) and ethyl isocyanide (**2b**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio

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93/7) **4f′** (17 mg, 75 μmol, 75%) as a colorless solid with minor amounts of (3a*R*,8*S*,8a*S*)-*N*-ethyl-3-oxohexahydro-1*H*,3*H*-azirino[1,2-*a*]pyrrolo[1,2-*d*]pyrazine-8-carboxamide.

Main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 1.12 (t, *J* = 7.2 Hz, 3H), 1.77−1.89(m, 3H),2.04−2.13 (m, 1H), 2.16−2.23 (m, 2H), 2.35−2.39 (m, 1H), 2.93−2.98 (m, 1H), 3.00−3.06 (m, 1H), 3.08−3.14 (m, 1H), 3.25−3.34 (m, 2H), 3.52 (d, *J* = 6.2 Hz, 1H), 6.41 (bs, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 14.9, 21.7, 21.9, 30.5, 33.9, 36.8, 54.4, 63.1, 63.9, 169.8, 183.0 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{11}H_{18}N_3O_2$ ([M + H]$^+$) 224.1399, found 224.1394; mp (mixture of diastereomers, $CDCl_3$) 82 °C.

*Methyl (3R,4S)-4-methyl-3-((3aS,8S,8aS)-3-oxohexahydro-1H,3H-azirino[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxamido)hexanoate (**4g′**).* According to **GP1** with (2*R*,4*R*,5*S*)-2-((*S*)-aziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (**3a**) (75.0 μmol), L-proline (150 μmol) and methyl (3*R*,4*S*)-3-isocyano-4-methylhexanoate(**2d**) (150 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 83/17) **4g′** (20 mg, 59 μmol, 39%) as a colorless solid with minor amounts of methyl (3*R*,4*S*)-4-methyl-3-((3a*S*,8*R*,8a*S*)-3-oxohexahydro-1*H*,3*H*-azirino-[1,2-*a*]pyrrolo[1,2-*d*]pyrazine-8-carboxamido)hexanoate.

Main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.81 (dd, *J* = 14.1, 7.1 Hz, 6H), 1.05−1.11 (m, 1H), 1.38−1.46 (m, 1H), 1.78−1.91 (m, 3H), 2.10−2.19 (m, 2H), 2.25 (dt, *J* = 4.2, 0.5 Hz, 1H), 2.39 (dd, *J* = 4.8, 0.5 Hz, 1H), 2.51(d, *J* = 5.6 Hz, 2H),2.93−2.98 (m, 1H), 3.06 (ddd, *J* = 6.1, 4.8, 4.2 Hz, 1H), 3.16−3.21 (m, 1H), 3.00−3.06 (m, 1H), 3.53 (d, *J* = 6.0 Hz, 1H), 3.66 (s, 3H), 4.09−4.15 (m, 1H), 6.83 (d, *J* = 9.2 Hz, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 11.1, 15.3, 21.7, 21.9, 25.8, 30.5, 35.8, 36.9, 37.7, 50.0, 51.8, 54.3, 63.3, 64.1, 169.0, 172.2, 183.1 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{17}H_{28}N_3O_4$ ([M + H]$^+$) 338.2080, found 338.2079; mp (mixture of diastereomers, $CDCl_3$) 116 °C.

*(3S,5R,6S)-3-Benzyl-N-ethyl-2-oxo-1,4-diazabicyclo[4.1.0]-heptane-5-carboxamide (**4f″**).* According to **GP1** with (2*R*,4*R*,5*S*)-2-((*S*)-aziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (**3a**) (50.0 μmol), L-phenylalanine (100 μmol) and ethyl isocyanide (**2b**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 12/88) **4f″** (13 mg, 48 μmol, 48%) as a colorless solid with minor amounts of (3*S*,5*S*,6*S*)-3-benzyl-*N*-ethyl-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamide.

Main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.73 (t, *J* = 7.3 Hz, 3H), 1.91(bs, 1H), 2.04 (d, *J* = 4.1 Hz, 1H), 2.54 (dd, *J* = 14.4, 11.1 Hz, 1H), 2.57 (d, *J* = 4.8 Hz, 1H), 2.80−2.89 (m, 1H), 2.95−3.10 (m, 2H), 3.21 (dd, *J* = 14.3, 3.2 Hz, 1H), 3.48 (t, *J* = 4.4 Hz, 1H), 3.58 (d, *J* = 4.4 Hz, 1H), 6.59 (bs, 1H), 7.17−7.36 (m, 5H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 14.3, 31.1, 33.9, 34.8, 34.9, 53.6, 57.8, 126.8, 2 × 128.5, 2 × 129.4, 138.2, 169.6, 184.9 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{15}H_{20}N_3O_2$ ([M + H]$^+$) 274.1556, found 274.1562; mp (mixture of diastereomers, $CDCl_3$) 124 °C.

*Methyl (3R,4S)-3-((3S,5R,6S)-3-benzyl-2-oxo-1,4-diazabicyclo-[4.1.0]heptane-5-carboxamido)-4-methylhexanoate (**4g″**).* According to **GP1** with (2*R*,4*R*,5*S*)-2-((*S*)-aziridin-2-yl)-3-oxa-1-azabicyclo-[3.1.0]hexan-4-ol (**3a**) (50.0 μmol), L-phenylalanine (100 μmol) and methyl (3*R*,4*S*)-3-isocyano-4-methylhexanoate (**2d**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 17/83) **4g″** (13 mg, 33 μmol, 33%) as a colorless liquid with minor amounts of methyl (3*R*,4*S*)-3-((3*S*,5*S*,6*S*)-3-benzyl-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamido)-4-methylhexanoate.

Main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.69 (d, *J* = 6.9 Hz, 3H), 0.78−0.89 (m, 4H), 1.14−1.25 (m, 2H), 1.64 (dd, *J* = 14.5, 9.8 Hz, 1H), 1.91(bs, 1H), 2.02 (d, *J* = 4.1, 1H), 2.22 (dd, *J* = 14.5, 3.8 Hz, 1H), 2.55(d, *J* = 4.7 Hz, 1H),2.59 (dd, *J* = 14.3, 10.2, Hz, 1H), 3.21 (dd, *J* = 14.3, 3.9 Hz, 1H), 3.26−3.34 (m, 1H), 3.43 (ddd, *J* = 4.7, 4.1, 1.6 Hz, 1H), 3.57 (bs, 1H), 3.60 (s, 3H), 4.00−4.09 (m, 1H), 6.87 (d, *J* = 10.1 Hz, 1H), 7.21−7.34 (m, 5H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 11.3, 15.2, 25.1, 31.1, 35.1, 35.2, 36.4, 38.4, 50.1, 51.7, 53.3, 56.8, 126.6, 2 × 128.6, 2 × 129.8, 138.2, 169.6, 171.9, 185.3 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{21}H_{30}N_3O_4$ ([M + H]$^+$) 388.2236, found 388.2244.

*(1S,3aS,8S,8aR)-N-(tert-Butyl)-1-methyl-3-oxohexahydro-1H,3H-azirino[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxamide (**8a′**).* According to **GP1** with (2*S*,4*S*,5*R*,6*S*)-6-methyl-2-((2*R*,3*S*)-3-methylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol(**6**) (50.0 μmol), L-proline (100 μmol) and *tert*-butyl isocyanide (**2a**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 63/37) **8a′** (10 mg, 37 μmol, 37%) as a colorless oil with (1*S*,3a*S*,8*R*,8a*R*)-*N*-(*tert*-butyl)-1-methyl-3-oxohexahydro-1*H*,3*H*-azirino[1,2-*a*]pyrrolo[1,2-*d*]pyrazine-8-carboxamide.

Main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 1.36 (s, 9H), 1.40 (d, *J* = 5.6 Hz, 3H), 1.78−1.88 (m, 3H), 2.22−2.28 (m, 2H), 2.85 (d, *J* = 8.7 Hz, 1H),2.96−3.03 (m, 2H), 3.09 (dd, *J* = 8.8, 2.9 Hz, 1H), 3.78 (dd, *J* = 9.1, 5.1 Hz, 1H), 6.45 (bs, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 17.3, 25.5, 3 × 28.7, 30.3, 41.2, 41.9, 47.4, 51.2, 62.2, 65.6, 167.3, 189.7 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{14}H_{24}N_3O_2$ ([M + H]$^+$) 266.1869, found 266.1874.

*(1S,3aS,8S,8aR)-N-Ethyl-1-methyl-3-oxohexahydro-1H,3H-azirino[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxamide (**8b′**).* According to **GP1** with (2*S*,4*S*,5*R*,6*S*)-6-methyl-2-((2*R*,3*S*)-3-methylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol(**6**) (50.0 μmol), L-proline (100 μmol) and ethyl isocyanide (**2b**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired *cis*-product **8b′** (5 mg, 21 μmol, 21%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 1.16 (t, *J* = 7.3 Hz, 3H), 1.41 (d, *J* = 5.6 Hz, 3H), 1.77−1.89 (m, 1H), 1.93−2.05 (m, 2H), 2.22−2.57 (m, 2H),2.91 (d, *J* = 8.7 Hz, 1H), 2.96−3.01 (m, 2H), 3.12 (ddd, *J* = 8.7, 2.4, 0.4 Hz, 1H), 3.27−3.40 (m, 2H), 3.78 (dd, *J* = 9.1, 5.2 Hz, 1H), 6.58 (bs, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 14.8, 17.3, 25.5, 30.2, 34.1, 41.2, 42.0, 47.5, 61.7, 65.6, 167.9, 189.7 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{12}H_{20}N_3O_2$ ([M + H]$^+$) 238.1556, found 238.1555.

*(1S,3aR,8R,8aS)-N-(tert-Butyl)-1-methyl-3-oxohexahydro-1H,3H-azirino[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxamide (**8c″**).* According to **GP1** with (2*R*,4*R*,5*S*,6*S*)-6-methyl-2 ((2*S*,3*S*)-3-methylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]-hexan-4-ol (**7**) (50.0 μmol), D-proline (100 μmol) and *tert*-butyl isocyanide (**2a**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired *cis*-product **8c″** (14 mg, 53 μmol, 53%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 1.20 (d, *J* = 6.1 Hz, 3H), 1.32 (s, 9H), 1.70−1.82 (m, 1H), 1.84−2.15 (m, 2H), 2.18−2.30 (m, 1H), 2.73−2.80 (m, 1H), 2.85−2.93 (m, 1H), 2.94−3.02 (m, 2H), 3.32 (dd, *J* = 9.0, 5.1 Hz, 1H), 3.58 (dd, *J* = 9.4, 4.1 Hz, 1H), 6.45 (bs, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 10.5, 24.8, 3 × 28.8, 29.8, 37.7, 37.7, 47.1, 51.1, 55.9, 65.9, 167.6, 187.0 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{14}H_{24}N_3O_2$ ([M + H]$^+$) 266.1869, found 266.1869; mp ($CDCl_3$) 93 °C.

*(1S,3aS,8S,8aS)-N-Ethyl-1-methyl-3-oxohexahydro-1H,3H-azirino[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxamide (**8d′**).* According to **GP1** with (2*R*,4*R*,5*S*,6*S*)-6-methyl-2-((2*S*,3*S*)-3-methylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (**7**) (50.0 μmol), L-proline (100 μmol) and ethyl isocyanide (**2b**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired *cis*-product **8d′** (18 mg, 74 μmol, 74%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 1.13 (td, *J* = 7.3, 0.8 Hz, 3H), 1.36 (dd, *J* = 6.2, 0.8 Hz, 3H), 1.80−1.91(m, 3H), 1.97−2.14 (m, 2H), 2.62−2.68 (m, 1H), 2.91−2.96 (m, 1H), 3.08 (ddd, *J* = 7.1, 4.9, 1.0 Hz, 1H), 3.22−3.28 (m, 1H), 3.29−3.40 (m, 2H), 3.60 (d, *J* = 7.1, 1H), 6.29 (bs, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 12.8, 14.7, 21.6, 21.6, 33.9, 40.0, 40.6, 55.3, 2 × 63.9, 168.7, 180.5 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{12}H_{20}N_3O_2$ ([M + H]$^+$) 238.1555, found 238.1553; mp ($CDCl_3$) 149 °C.

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*(1S,3aR,8R,8aS)-N-Ethyl-1-methyl-3-oxohexahydro-1H,3H-azirino[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxamide (**8d″**).* According to **GP1** with (2*R*,4*R*,5*S*,6*S*)-6-methyl-2-((2*S*,3*S*)-3-methylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (**7**) (50.0 μmol), D-proline (100 μmol) and ethyl isocyanide (**2b**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 92/8) **8d″** (14 mg, 58 μmol, 58%) as a colorless solid with minor amounts of (1*S*,3a*R*,8*S*,8a*S*)-*N*-ethyl-1-methyl-3-oxohexahydro-1*H*,3*H*-azirino[1,2-*a*]pyrrolo[1,2-*d*]pyrazine-8-carboxamide.

Main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 1.18 (t, *J* = 7.3 Hz, 3H), 1.28 (d, *J* = 6.1 Hz, 3H), 1.77−1.87(m, 1H), 1.92−2.03 (m, 2H), 2.27−2.36 (m, 1H), 2.87 (qd, *J* = 6.1, 5.1 Hz, 1H), 2.93−2.98 (m, 1H), 3.01−3.07 (m, 1H), 3.11 (d, *J* = 9.1 Hz, 1H), 3.29−3.43 (m, 3H), 3.67 (dd, *J* = 9.4, 4.3 Hz, 1H), 6.65 (bs, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 10.6, 15.0, 25.0, 30.0, 34.3, 37.8, 37.9, 47.4, 55.7, 66.1, 168.3, 187.1 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{12}H_{20}N_3O_2$ ([M + H]$^+$) 238.1555, found 238.1549; mp (mixture of diastereomers, $CDCl_3$) 96 °C.

*(1S,3aR,8R,8aS)-1-Methyl-N-((S)-2-methyl-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propyl)-3-oxohexahydro-1H,3H-azirino[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxamide (**8e″**).* According to **GP1** with (2*R*,4*R*,5*S*,6*S*)-6-methyl-2-((2*S*,3*S*)-3-methylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (**7**) (50.0 μmol), D-proline (100 μmol) and (*S*)-1-(1-isocyano-2-methylpropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**2c**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired *cis*-product **8e″** (17 mg, 43 μmol, 43%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.80 (s, 3H), 0.87 (dd, *J* = 13.6, 6.9 Hz, 6H), 1.27 (d, *J* = 6.1 Hz, 3H), 1.73−1.85(m, 1H), 1.89−2.02 (m, 2H), 2.14−2.23 (m, 1H), 2.30−2.39 (m, 1H), 2.80−2.94 (m, 2H),3.17 (d, *J* = 9.0 Hz, 1H), 3.20−3.25 (m, 1H), 3.43 (dd, *J* = 9.0, 5.1 Hz, 1H), 3.68 (dd, *J* = 9.5, 4.3 Hz, 1H), 3.86 (s, 6H), 4.11 (dd, *J* = 10.5, 3.3 Hz, 1H), 6.89 (d, *J* = 10.4 Hz, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 10.5, 14.4, 16.9, 21.0, 24.9, 27.6, 29.9, 30.6, 37.8, 37.8, 46.9, 54.9, 56.4, 65.5, 3 × 72.5, 108.5, 168.8, 187.2 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{20}H_{32}N_3O_5$ ([M + H]$^+$) 394.2342, found 394.2347; mp ($CDCl_3$) 185 °C.

*(1S,3aR,8R,8aS)-N-((R)-1-(Benzylamino)-4-methyl-1-oxopentan-3-yl)-1-methyl-3-oxohexahydro-1H,3H-azirino[1,2-a]pyrrolo[1,2-d]-pyrazine-8-carboxamide (**8f**).* According to **GP1** with (2*R*,4*R*,5*S*,6*S*)-6-methyl-2-((2*S*,3*S*)-3-methylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]-hexan-4-ol (**7**) (50.0 μmol), D-proline (100 μmol) and (*R*)-*N*-benzyl-3-isocyano-4-methylpentanamide (**2e**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired *cis*-product **8f** (17 mg, 42 μmol, 42%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.92 (t, *J* = 6.7 Hz, 6H), 1.23 (d, *J* = 6.1 Hz, 4H), 1.75−1.95(m, 4H), 2.22−2.33 (m, 1H), 2.44−2.56 (m, 2H), 2.71−2.84 (m, 2H), 2.96−3.03 (m, 1H),3.07 (d, *J* = 9.1 Hz, 1H), 3.22 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.65 (dd, *J* = 9.5, 4.3 Hz, 1H), 3.98−4.05 (m, 1H), 4.35−4.45 (m, 2H), 6.49 (t, *J* = 5.6 Hz, 1H), 7.23−7.32 (m, 4H), 7.45 (d, *J* = 9.5 Hz, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 10.6, 19.2, 19.6, 25.0, 29.9, 31.8, 2 × 37.8, 38.4, 43.7, 47.2, 52.2, 55.5, 66.2, 127.7, 2 × 128.0, 2 × 128.8, 138.2, 168.5, 170.8, 187.2 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{23}H_{33}N_4O_3$ ([M + H]$^+$) 413.2553, found413.2541; mp ($CDCl_3$) 134 °C.

*(3R,5S,6R,7S)-3-Benzyl-7-methyl-N-((S)-2-methyl-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propyl)-2-oxo-1,4-diazabicyclo-[4.1.0]heptane-5-carboxamide (**8g**).* According to **GP1** with (2*R*,4*R*,5*S*,6*S*)-6-methyl-2-((2*S*,3*S*)-3-methylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol(**7**) (50.0 μmol), D-phenylalanine (100 μmol) and(*S*)-1-(1-isocyano-2-methylpropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**2c**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired product (*cis*/*trans* ratio 7/93) **8g** (15 mg, 33 μmol, 33%) as a colorless solid with minor amounts of (3*R*,5*R*,6*R*,7*S*)-3-benzyl-7-methyl-*N*-((*S*)-2-methyl-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propyl)-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamide.

Main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.77 (s, 3H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.87−0.90 (m, 4H), 1.38 (d, *J* = 6.2 Hz, 3H), 2.12−2.23 (m, 1H), 2.69−2.76 (m, 1H),3.06 (dd, *J* = 13.9, 9.3 Hz, 1H), 3.12 (dd, *J* = 7.1 Hz, 4.8 Hz, 1H),3.18 (dd, *J* = 13.9, 6.4 Hz, 1H), 3.60 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.77−3.84 (m, 6H),4.06 (dd, *J* = 10.2, 3.2 Hz, 1H), 4.44 (d, *J* = 7.1 Hz, 1H), 6.36 (d, *J* = 10.2 Hz, 1H), 7.21−7.36 (m, 5H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 11.9, 14.5, 17.2, 21.2, 27.8, 30.7, 35.8, 37.9, 38.2, 48.9, 57.0, 60.3, 3 × 72.6, 108.6, 127.1, 2 × 129.0, 2 × 129.2, 136.5, 170.0, 182.3 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{24}H_{34}N_3O_5$ ([M + H]$^+$) 444.2499, found 444.2505; mp (mixture of diastereomers, $CDCl_3$) 148 °C.

*Methyl (3R,4S)-3-((3R,5S,6R,7S)-3-benzyl-7-methyl-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamido)-4-methylhexanoate (**8h**).* According to **GP1** with (2*R*,4*R*,5*S*,6*S*)-6-methyl-2-((2*S*,3*S*)-3-methylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol(**7**) (50.0 μmol), D-phenylalanine (100 μmol) andmethyl (3*R*,4*S*)-3-isocyano-4-methylhexanoate (**2d**) (100 μmol). FC purification (ethyl acetate/hexanes 50/50 to ethyl acetate/hexanes 100/0) afforded the desired *trans*-product **8h** (17 mg, 41 μmol, 41%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 0.84 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 7.3 Hz, 3H), 1.03−1.22 (m, 1H), 1.19−1.32 (m, 1H), 1.34 (d, *J* = 6.2 Hz, 2H), 1.37−1.45 (m, 1H), 1.53−1.62 (m, 1H),1.93 (bs, 1H), 2.36−2.48 (m, 2H), 2.74 (qd, *J* = 6.2, 4.8 Hz, 1H), 3.05 (dd, *J* = 13.9, 9.9 Hz, 1H), 3.12−3.21 (m, 2H), 3.57 (s, 3H), 3.58−3.64 (m, 1H), 4.10−4.16 (m, 1H), 4.34−4.39 (m, 1H), 6.89 (d, *J* = 9.2 Hz, 1H), 7.21−7.38 (m, 5H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$, 100 K) δ = 11.3, 11.8, 15.0, 25.8, 35.4, 35.8, 37.6, 38.0, 38.4, 48.8, 50.4, 51.8, 60.1, 127.1, 2 × 129.0, 2 × 129.0, 136.0, 169.5, 172.4, 181.9 ppm; HRMS (DART-TOF) Exact mass calculated for $C_{22}H_{32}N_3O_4$ ([M + H]$^+$) 402.2393, found 402.2388.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00471.

Copies of ^{1}H, ^{13}C, and 2-D NMR data for all products, as well as complete computational calculations. (PDF)

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Notes

The authors declare no competing financial interest.

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