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Synthesis and Regioselective Functionalization of Piperazin-2-ones Based on Phe-Gly Pseudodipeptides

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The synthesis of 1,4-unsubstituted piperazin-2-ones by one-pot reductive cyclization of PheΨ[CH(CN)NH]Gly pseudodipeptides is described. Studies on the reactivity of the piperazin-2-one ring showed a higher reactivity at the N^4 position than at the N^1 position. The stepwise regioselective functionalization of piperazin-2-one derivatives showed great potential for molecular diversity generation.

Introduction

The piperazine ring is recognized as a privileged scaffold due to its recurrent presence in biologically active compounds.[1] At present there are 165 drug entries for this heterocycle in the DrugBank database.[2] Specifically, the piperazin-2-one system is present in diverse natural products, such as pseudotheonamides,[3] marcfortine B,[4] ergopeptines[5] and guadinomine C_2[6] In addition, the piperazin-2-one skeleton has been used to introduce conformational restriction in peptides and in the design of peptidomimetics such as neurokinin,[7] cholecystokinin[8] and neuropeptide S[9] and of fibrinogen antagonists,[10] melanocortin-4 receptor agonists[7] and inhibitors of different proteases[11] Furthermore, this scaffold has been proposed as a mimetic of γ turn[12] and α helix[13] peptide secondary structures. The development of new approaches to the synthesis of chiral piperazin-2-one derivatives with diverse substitution at different ring positions to increase molecular diversity in medicinal chemistry is therefore of particular significance. In this context, different methods for the construction of piperazin-2-ones have been reported and have recently been reviewed.[1,14]

As part of our ongoing medicinal chemistry project devoted to the search for piperazin-2-one-based peptidomimetics as PAR1 antagonists, here we report the synthesis of 1,4-unsubstituted piperazin-2-ones derived from Phe-Gly dipeptides and their regioselective functionalization at the N^1 and N^4 positions, including the synthesis of fused bicyclic derivatives.

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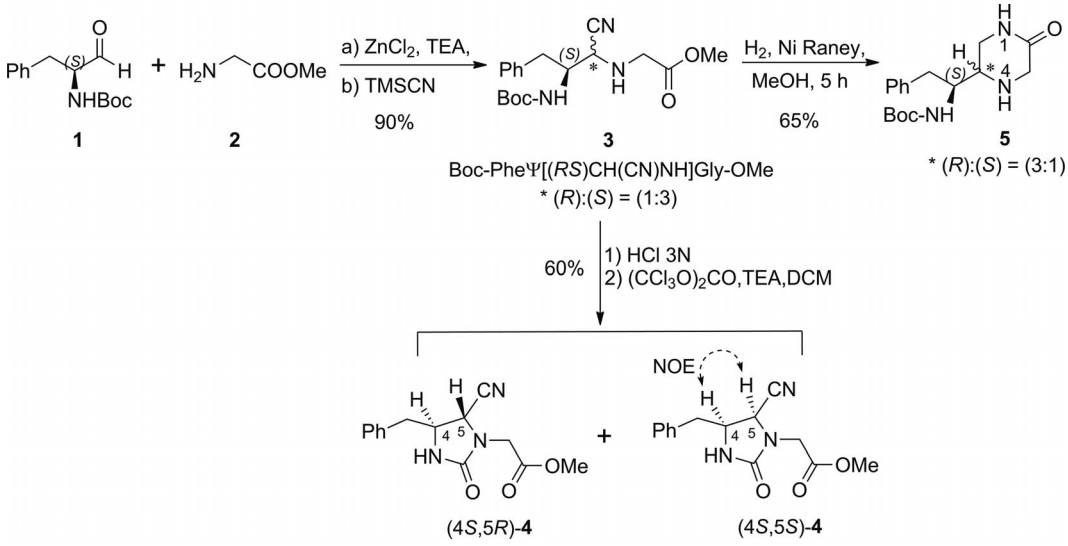
Results and Discussion

Our synthetic approach for building the piperazin-2-one ring involves two key steps: a modified Strecker reaction for the synthesis of cyanomethylamino pseudodipeptides, followed by a reductive cyclization. To study this approach, the pseudodipeptides Boc-PheΨ[(*RS*)CH(CN)NH]Gly-OMe (**3**, Scheme 1) [15] were prepared by treatment of the *N*-protected α-amino aldehyde **1** with the amino acid methyl ester **2** and TMSCN, by the methodology developed in our group.[16] The pseudodipeptide **3** was obtained as an epimeric mixture at the stereogenic centre of the peptide bond surrogate [(1*R*)/(1*S*) 1:3], which could not be resolved. Consistently with previous results, no epimerization was observed at the chiral centre of the α-amino aldehyde.[12a,16–17]

To assign the configurations at the new chiral centre in the two epimers of **3**, they were transformed into the corresponding mixture of imidazolidin-2-ones **4** (Scheme 1) by a sequence of *N*-Boc removal and treatment with bis(trichloromethy1)carbonate. In the ^{1}H NMR spectrum of the epimeric mixture, the major isomer (5*S*)-**4** showed a $J_{4,5}$ value of 8 Hz consistent with a H^4,H^5 relative *cis* orientation, whereas in the minor isomer (5*R*)-**4** the value of this constant was 4.5 Hz, indicative of a H^4,H^5 *trans* relative orientation.[16] Furthermore, this assignment was confirmed by the stronger NOE effect between the H^4,H^5 protons observed for the major isomer in the NOESY 1D spectrum of the mixture (Scheme 1).

Reductive cyclization of pseudodipeptides **3** by catalytic hydrogenation with in situ lactamization, in the presence of Raney Ni as catalyst,[17] led to the 5-substituted piperazin-2-ones **5** (Scheme 2, below) in 65% yield. The diastereomeric ratio remained unchanged in this reductive cyclization [(*R*)/(*S*) 3:1].[18]

To explore access to molecular diversity in the piperazin-2-one scaffold, an exploratory study on the reactivity at the

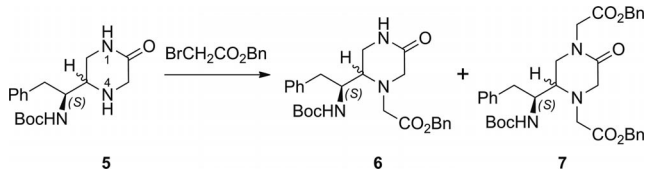


Scheme 1. Synthesis and configuration assignment of piperazin-2-ones.

N^1 and N^4 positions was carried out. Firstly, we examined regioselective alkylation. To this end, alkylation of the epimeric mixture of **5** with benzyl bromoacetate with use of different bases and reaction conditions was studied.

As shown in Table 1, the base plays a critical role in the monoalkylation/dialkylation product ratio. When NaH (Entry 1) and Cs_2CO_3 (Entry 2) were used, the reaction took more than 5 d, and the monoalkylated piperazin-2-ones **6** were obtained together with variable amounts of the dialkylated products **7**. When K_2CO_3 (Table 1, Entry 3) was used, however, epimers **6** were obtained as the sole reaction products. To decrease the reaction time, we studied the reaction under microwave heating conditions at 100 °C and 150 °C in the presence of K_2CO_3 as alkylating reagent. Interestingly, under these condition, with heating at 150 °C for 10 min, the desired 4-alkylated piperazin-2-ones **6** were obtained regiospecifically in 95% yield (Table 1, Entry 8).

Table 1. Regioselective alkylation at N^4.

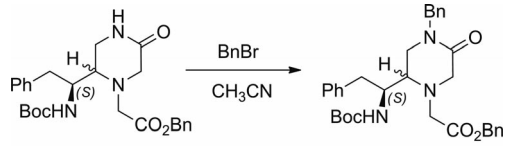


Entry	Base	Equiv. Base	T [°C]	t	Yield [%][a] 6	7
1	NaH	1.1	60	6 d	43[b]	5[b]
2	Cs_2CO_3	1.1	60	5 d	67[b]	17[b]
3	K_2CO_3	1.1	60	3 d	89[b]	0
4	K_2CO_3	1.1	100 (MW)[c]	5 min	63	0
5	K_2CO_3	1.1	150 (MW)	5 min	70	0
6	K_2CO_3	1.1	150 (MW)	20 min	78	0
7	K_2CO_3	1.5	150 (MW)	10 min	90	0
8	K_2CO_3	2	150 (MW)	10 min	95	1

[a] Calculated by HPLC [Sunfire C_{18} (4.6 × 150 mm, 3.5 μm), gradient 10–100% A in B for 30 min]. [b] Isolated compounds. [c] MW: microwave heating.

In view of the low N^1 reactivity, N^1-alkylation of **6** with BnBr under microwave heating conditions at 150 °C in the presence of different bases was also studied (Table 2), with the reaction being checked by HPLC-MS after 10, 20 and 30 min. After 30 min, the reactions were complete, except in the case of the use of K_2CO_3 (Table 2, Entry 1), in which the starting material remained unchanged. The low yields obtained in the presence of NaH (Table 2, Entry 2) or DBU (Table 2, Entry 7) were due to the formation of high percentages of decomposition products. The best bases were Cs_2CO_3 (Table 2, Entry 3) and phosphazene base P1-*t*Bu (Table 2, Entry 6), which led to the piperazin-2-ones **8** in 70–75% yield.

Table 2. Reaction conditions for the N^1-benzylation of **6**.



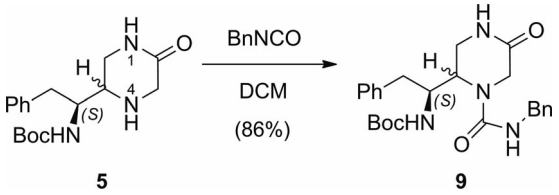
Entry	Base	**8**, yield /%[a]
1	K_2CO_3	0[b]
2	NaH	28[c]
3	Cs_2CO_3	95 (70)[d]
4	BEMP	93
5	BTPP	90
6	phosphazene base P1-*t*Bu	98 (75)[d]
7	DBU	0[c]

[a] Calculated by HPLC [Sunfire C_{18} (4.6 × 150 mm, 3.5 μm), gradient 10–100% A in B for 30 min]. [b] Starting material remained unchanged. [c] Starting material decomposition. [d] Isolated compound.

Although, it was not possible to resolve the epimeric mixtures, the epimeric ratio remained constant through the different alkylation reactions. The fact that no racemization

had occurred was unequivocally demonstrated by further debenzylation and subsequent coupling with different amino acids.[19]

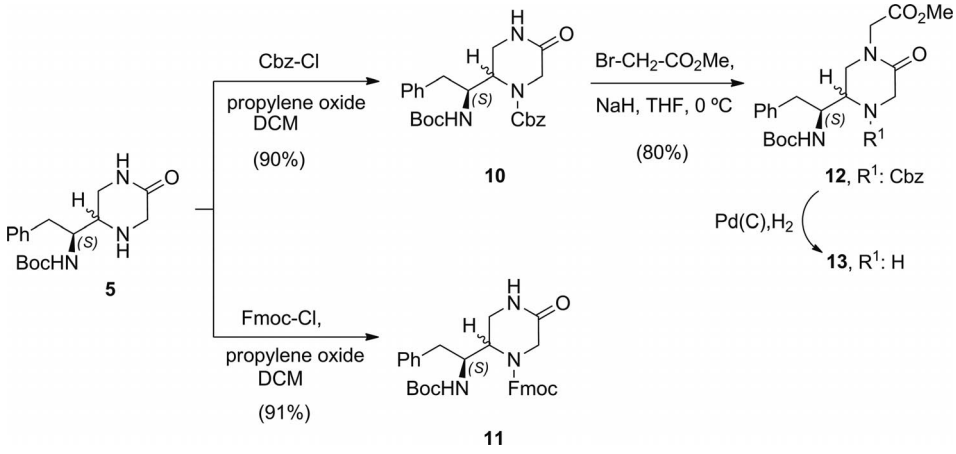
After the alkylation studies, we explored the reaction of the piperazin-2-ones **5** with benzyl isocyanate with the aim of preparing urea derivatives. As shown in Scheme 2, this reaction provided the corresponding ureas **9** regiospecifically in good yields (86%).



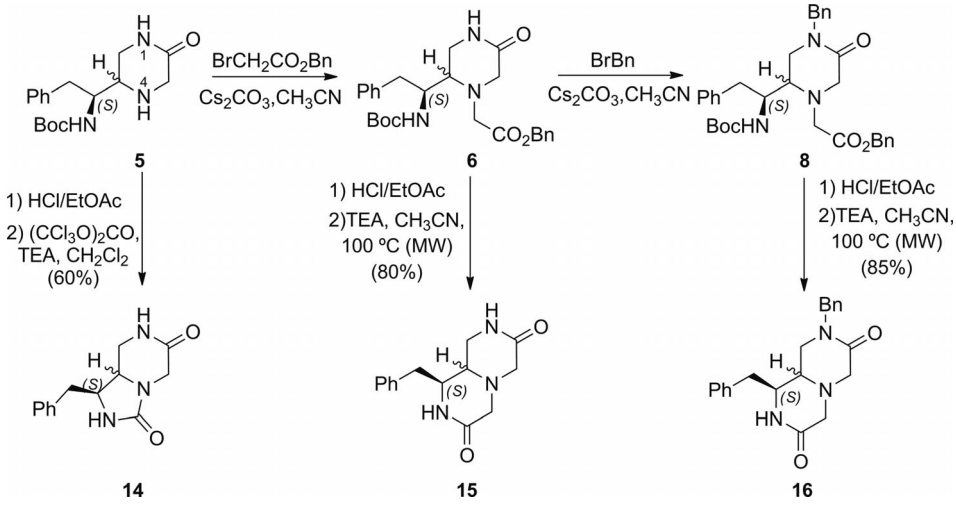
Scheme 2. Synthesis of ureas.

In view of the higher reactivity of the N^4 position, protection of this position was studied as a strategy for regioselective functionalization of the N^1 in preference to the N^4 position. To this end, the benzyloxycarbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc) groups were chosen as protecting groups. As shown in Scheme 3, treatment of the piperazin-2-ones **5** with Cbz-Cl or Fmoc-Cl gave the corresponding N^4-protected derivatives **10** and **11** regiospecifically in excellent yields. Next, the N^1-alkylation of **10** under the optimized conditions (Cs_2CO_3 at 150 °C, MW; see above, Table 2, Entry 3) was tried. Under these conditions, the N^1-alkylated piperazin-2-ones **12** were detected by HPLC-MS (55% yield), together with the Cbz-deprotected byproduct (45%). After a new study of reaction conditions (base, temperature and solvent), the Cbz removal was avoided and the N^1-alkylated derivatives **12** were obtained regioselectively in 80% yield by use of NaH as base in THF/DMF (9:1) at 0 °C. Next, Pd(C)-catalysed hydrogenolysis of **12**, at room temperature, gave the corresponding 4-deprotected piperazin-2-ones **13** in good yield (78%).

Finally, because skeletal diversity is one of the key factors for molecular diversity, we studied the potential of the stepwise N^1,N^4-functionalization to transform the piperazine ring into fused bicyclic scaffolds. Thus, as shown in Scheme 4, *N*-Boc removal from **5**, followed by treatment with triphosgene in the presence of TEA, led to the imidazo[1,5-*a*]pyrazines **14** (60% yield). On the other hand, *N*-



Scheme 3. N^4-Protection and N^1-alkylation.



Scheme 4. Building of bicyclic skeletons.

Boc removal from the 4-(benzyloxycarbonylmethyl)piperazin-2-ones **6** and **8**, followed by microwave heating in the presence of TEA, led to the pyrazino[1,2-*a*]pyrazines **15** (80% yield) and **16** (85% yield), respectively. These new skeletons contain accessible diversity points that could allow the further incorporation of additional functionalities.

Conclusions

In summary, we have outlined an easy methodology to obtain N^1,N^4-unsubstituted piperazin-2-ones in one-pot fashion from PheΨ[(*RS*)CH(CN)NH]Gly pseudodipeptides, which are readily available through a three-component Strecker reaction. Study of the reactivity in the piperazin-2-one ring has shown that through appropriate control of reaction conditions, regioselective functionalization of either the N^1 or the N^4 position is possible. Furthermore, piperazin-2-ones as described here are good intermediates for the building of new bicyclic skeletons. The application of these methodologies to the field of protein-ligand modulators is in progress and will be reported elsewhere.

Experimental Section

General Method: All reagents were of commercial quality. Solvents were dried and purified by standard methods. Analytical TLC was performed on aluminium sheets coated with a layer (0.2 mm) of silica gel (60 F^{254}). Silica gel 60 (230–400 mesh) was used for flash chromatography. Analytical HPLC was performed with a Sunfire C_{18} (4.6 × 150 mm, 3.5 μm) column, a flow rate of 1 mL min^{-1} and a tuneable UV detector set at 214 nm. A 10–100% gradient of CH_3CN (solvent A) in 0.05% TFA in H_2O (solvent B) over 30 min was used as mobile phase. ^{1}H NMR spectra were recorded at 300 or 400 MHz, with TMS as reference, and ^{13}C NMR spectra were recorded at 75 or 100 MHz. The NMR spectra assignment was based on COSY, HSQC, and HMBC spectra. ESI-MS was performed, in positive mode with MeOH as solvent. MW experiments were carried out with an Emrys™ Synthesizer MW reactor (Biotage AB, surface IR sensor).

Boc-PheΨ[(*RS*)CH(CN)NH]Gly-OMe (3): TEA (1.1 mL, 7.96 mmol) was added to a solution of H-Gly-OMe·HCl (1.00 g, 7.96 mmol) in MeOH (40 mL). After 15 min stirring at room temperature, the mixture was cooled to –20 °C and $ZnCl_2$ (542 mg, 3.98 mmol) was added, followed by Boc-Phe-H[20] (992 mg, 3.98 mmol). The solution was stirred for 1 h at –20 °C, TMSCN was then added (896 μL, 7.16 mmol), and the mixture was stirred at 0 °C for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (50 mL). The solution was washed with H_2O (2 × 25 mL) and brine (25 mL) and dried with Na_2SO_4, and the solvents were evaporated to dryness to give the epimeric mixture of α-aminonitriles **3** (*R*/*S* = 1:3) as a foam (1.24 g, 90%). HPLC: t_R = 21.84 min **[(*R*)-3]** and 21.65 min [(*S*)-**3**]. ^{1}H NMR (400 MHz, $CDCl_3$), epimer (*R*)-**3**: δ = 1.35 (s, 9 H), 2.84 (dd, *J* = 8.5, 14 Hz, 1 H), 3.12 (dd, *J* = 6, 14 Hz, 1 H), 3.50 (m, 1 H), 3.70 (d, *J* = 6 Hz, 1 H), 3.72 (s, 3 H), 4.14 (m, 1 H), 4.83 (m, 1 H), 7.11–7.29 (m, 5 H) ppm. Epimer (*S*)-**3:** δ = 1.36 (s, 9 H), 2.90 (dd, *J* = 7.5, 14 Hz, 1 H), 2.96 (dd, *J* = 9.5, 14 Hz, 1 H), 3.5 (m, 2 H), 3.69 (s, 3 H), 3.72 (d, *J* = 6 Hz, 1 H), 4.24 (m, 1 H), 4.83 (m, 1 H), 7.11–7.29 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$), epimer (*R*)-**3**: δ = 28.1, 38.2, 48.3, 52.0, 53.4, 80.3, 118.1, 126.9, 128.6, 129.1, 136.0, 155.5, 171.3 ppm. Epimer (*S*)-**3**: δ = 28.1, 38.2, 48.4, 52.0, 53.9, 80.3, 117.5, 127.0, 128.7, 129.0, 136.0, 155.5, 171.0 ppm. ES-MS: *m*/*z* = 348.4 [M + 1]$^+$. $C_{18}H_{25}N_3O_4$ (347.41): calcd. C 62.23, H 7.25, N 12.10; found C 62.21, H 7.19, N 12.01.

(4*S*,5*RS*)-5-Cyano-1-(methoxycarbonylmethyl)-4-phenylmethylimidazolidin-2-one (4): The epimeric mixture of α-aminonitriles **3** (*R*/*S* 1:3, 100 mg, 0.28 mmol) was dissolved in a solution of HCl (3.4 N) in EtOAc (5 mL) and the mixture was stirred at room temperature for 30 min. Afterward, the solvent was evaporated to dryness, the residue was dissolved in CH_3CN/H_2O (1:3, 2 mL), and the solution was lyophilized. The residue was dissolved in dichloromethane (10 mL), and TEA (78 μL, 0.56 mmol) was added. After the system had been stirred at 0 °C for 15 min, triphosgene (33 mg, 0.11 mmol) and TEA (93 μL, 0.67 mmol) were added, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with dichloromethane (10 mL), washed with H_2O (2 × 5 mL) and brine (5 mL) and dried with Na_2SO_4, and the solvents were evaporated to dryness. The residue was purified by flash chromatography, with a 0–15% MeOH gradient in dichloromethane as mobile phase, to afford an epimeric mixture of 2-oxoimidazolidines **4** [(5*R*)/(5*S*) 1:3] as a foam (46 mg, 60%). HPLC: 15.62 min [(5*R*)-**4**] and 15.94 min [(5*S*)-**4**]. ^{1}H NMR (400 MHz, $CDCl_3$), epimer (5*R*)-**4**: δ = 2.96 (m, 2 H), 3.69 (d, *J* = 18.5 Hz, 1 H), 3.79 (s, 3 H), 4.12 (m, 1 H), 4.51 (d, *J* = 18.5 Hz, 1 H), 4.56 (d, *J* = 4.5 Hz, 1 H), 5.06 (s, 1 H), 7.21–7.40 (m, 5 H) ppm. Epimer (5*S*)-**4**: δ = 3.04 (dd, *J* = 9.5, 13.5 Hz, 1 H), 3.16 (dd, *J* = 5, 13.5 Hz, 1 H), 3.71 (d, *J* = 18.5 Hz, 1 H), 3.76 (s, 3 H), 4.19 (m, 1 H), 4.55 (d, *J* = 18.5 Hz, 1 H), 4.86 (s, 1 H), 4.91 (d, *J* = 8 Hz, 1 H), 7.21–7.40 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$), epimer (5*R*)-**4**: δ = 41.0, 42.5, 50.9, 52.5, 55.9, 116.0, 127.6, 128.5, 129.2, 134.8, 158.4, 169.2 ppm. Epimer (5*S*)-**4**: δ = 38.7, 42.9, 51.8, 52.5, 52.9, 114.3, 127.6, 128.5, 129.2, 135.2, 158.7, 169.2 ppm. ES-MS: *m*/*z* = 274.4 [M + 1]$^+$. $C_{14}H_{15}N_3O_3$ (273.29): calcd. C 61.53, H 5.53, N 15.38; found C 61.42, H 5.39, N 15.14.

(5*RS*)-5-[(1*S*)-1-*tert*-Butoxycarbonylamino-2-phenylethyl]piperazin-2-one (5): Raney Ni (1.50 g) was added to a solution of **3** [(2*R*)/(2*S*) 1:3, 1.00 g, 2.88 mmol] in MeOH (15 mL) and the mixture was hydrogenated at 1 atm of H_2 and room temperature for 5 h. Afterwards, the reaction mixture was filtered through celite and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography, with a 0–6% MeOH gradient in dichloromethane as mobile phase, to afford the epimeric mixture of piperazin-2-ones **5** [(5*R*)/(5*S*) 3:1] as a white solid (598 mg, 65%). HPLC: t_R = 12.04 min [(5*R*)-**5**] and 12.34 min [(5*S*)-**5**]. ^{1}H NMR (400 MHz, $CDCl_3$), epimer (5*R*)-**5**: δ = 1.36 (s, 3 H), 2.90 (m, 1 H), 2.92 (m, 1 H), 2.97 (dd, *J* = 5, 14 Hz, 1 H), 3.24, 3.30 (m, 2 H), 3.48 (d, *J* = 18 Hz, 1 H), 3.60 (d, *J* = 18 Hz, 1 H), 3.88 (m, 1 H), 6.13 (s, 1 H), 7.11–7.37 (m, 5 H) ppm. Epimer (5*S*)-**5**: δ = 1.38 (s, 3 H), 2.90 (m, 3 H), 3.22, 3.40 (m, 2 H), 3.42 (d, *J* = 17.5 Hz, 1 H), 3.58 (d, *J* = 17.5 Hz, 1 H), 3.90 (m, 1 H), 6.02 (s, 1 H), 7.11–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$), epimer (5*R*)-**5**: δ = 28.4, 37.2, 45.6, 49.1, 53.4, 54.8, 80.0, 126.8, 128.8, 129.5, 137.3, 155.9, 169.9 ppm. Epimer (5*S*)-**5**: δ = 28.4, 38.9, 45.6, 49.3, 52.8, 53.4, 80.0, 126.9, 128.9, 129.3, 137.5, 155.6, 170.2 ppm. ES-MS: *m*/*z* = 320.2 [M + 1]$^+$. $C_{17}H_{25}N_3O_3$ (319.40): calcd. C 63.93, H 7.89, N 13.16; found C 63.76, H 8.04, N 13.31.

(5*RS*)-4-Benzyloxycarbonylmethyl-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-phenylethyl]piperazin-2-one (6): Benzyl bromoacetate (68 μL, 0.34 mmol) and K_2CO_3 (47 mg, 0.34 mmol) were added under argon to a solution of **5** [(5*R*)/(5*S*) 3:1, 100 mg, 0.31 mmol] in anhydrous CH_3CN (5 mL), and the mixture was stirred for 3 d at 60 °C. Afterwards, the solvent was removed under reduced pressure

and the residue was dissolved in dichloromethane (100 mL). The solution was washed with H_2O (2× 25 mL) and brine (25 mL) and dried with Na_2SO_4, and the solvents were evaporated to dryness. The residue was purified by flash chromatography, with 0–6% MeOH gradient in dichloromethane as mobile phase, to afford the epimeric mixture **6** [(5*R*)/(5*S*) 3:1] as a foam (131 mg, 90%). HPLC: t_R = 21.41 min. ^{1}H NMR (400 MHz, $CDCl_3$), epimer (5*R*)-**6**: δ = 1.34 (s, 3 H), 2.94 (m, 3 H), 3.35 (m, 1 H), 3.44 (d, *J* = 18 Hz, 1 H), 3.45 (m, 1 H), 3.50 (m, 2 H), 3.66 (d, *J* = 18 Hz, 1 H), 4.02 (m, 1 H), 4.45 (d, *J* = 8 Hz, 1 H), 5.16 (s, 2 H), 6.29 (m, 1 H), 7.10–7.41 (m, 10 H) ppm. Epimer (5*S*)-**6**: δ = 1.36 (s, 3 H), 2.86 (m, 1 H), 2.94 (m, 2 H), 3.28 (m, 1 H), 3.44 (m, 1 H), 3.45 (m, 1 H), 3.50 (m, 2 H), 3.64 (d, *J* = 17.5 Hz, 1 H), 3.91 (m, 1 H), 5.02 (d, *J* = 8 Hz, 1 H), 5.14 [d, *J* = 5 Hz, 2 H], 6.25 (m, 1 H), 7.10–7.41 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$), epimer (5*R*)-**6**: δ = 28.2, 37.6, 40.7, 51.4, 52.8, 53.9, 58.0, 66.7, 79.8, 126.6, 128.5, 128.6, 129.4, 135.3, 137.2, 155.4, 169.4, 170.2 ppm. Epimer (5*S*)-**6**: δ = 28.3, 38.4, 40.7, 51.4, 52.4, 54.1, 58.0, 66.7, 79.8, 126.6, 128.5, 128.6, 129.2, 135.3, 137.4, 155.4, 169.4, 170.4 ppm. ES-MS: *m*/*z* = 468.4 [M + 1]$^+$. $C_{26}H_{33}N_3O_5$ (467.56): calcd. C 66.79, H 7.11, N 8.99; found C 66.70, H 7.21, N 9.08.

(5*RS*)-1-Benzyl-4-benzyloxycarbonylmethyl-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-phenylethyl]piperazin-2-one (8): Benzyl bromide (78 µL, 0.66 mmol) and Cs_2CO_3 (215 mg, 0.66 mmol) were added under argon to a solution of **6** [(5*R*)/(5*S*) 3:1, 100 mg, 0.22 mmol) in anhydrous CH_3CN (5 mL), and the mixture was stirred for 30 min at 150 °C with MW heating. Afterwards, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc (100 mL). The solution was washed with H_2O (2× 25 mL) and brine (25 mL) and dried with Na_2SO_4, and the solvents were evaporated to dryness. The residue was purified by flash chromatography, with 20–50% EtOAc gradient in hexane as mobile phase, to afford the epimeric mixture **8** [(5*R*)/(5*S*) 3:1] as a foam (86 mg, 70%). HPLC: t_R = 26.61 min. ^{1}H NMR (300 MHz, $CDCl_3$), epimer (5*R*)-**8**: δ = 1.32 (s, 3 H), 2.74 (m, 2 H), 2.95 (m, 1 H), 3.19 (dd, *J* = 7.5, 12.5 Hz, 1 H), 3.31 (dd, *J* = 5, 12.5 Hz, 1 H), 3.40 (d, *J* = 17 Hz, 1 H), 3.57 (m, 2 H), 3.61 (d, *J* = 17 Hz, 1 H), 3.97 (m, 1 H), 4.25 (d, *J* = 9 Hz, 1 H), 4.45 (d, *J* = 14.5 Hz, 1 H), 4.73 (d, *J* = 14.5 Hz, 1 H), 5.13 (s, 2 H), 7.10–7.40 (m, 15 H) ppm. Epimer (5*S*)-**8**: δ = 1.34 (s, 3 H), 2.74 (m, 2 H), 2.95 (m, 1 H), 3.17 (m, 1 H), 3.33 (m, 1 H), 3.40 (m, 1 H), 3.57 (m, 2 H), 3.61 (m, 1 H), 3.75 (m, 1 H), 4.26 (d, *J* = 9 Hz, 1 H), 4.41 (m, 1 H), 4.63 (m, 1 H), 5.15 (s, 2 H), 7.10–7.40 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$), epimer (5*R*)-**8**: δ = 28.2, 37.6, 44.6, 49.7, 51.2, 52.8, 54.4, 57.9, 66.8, 79.8, 126.7, 127.9, 128.6, 128.7, 128.9, 129.4, 135.4, 136.4, 137.2, 155.2, 167.2, 170.2 ppm. Epimer (5*S*)-**8**: δ = 28.2, 37.6, 45.2, 49.8, 51.2, 52.8, 54.4, 58.2, 66.7, 79.8, 126.7, 127.9, 128.4, 128.5, 128.6, 129.3, 134.4, 136.4, 137.2, 155.2, 168.3, 170.3 ppm. ES-MS: *m*/*z* = 558.2 [M + 1]$^+$. $C_{33}H_{39}N_3O_5$ (557.69): calcd. C 71.07, H 7.05, N 7.53; found C 71.19, H 6.92, N 7.62.

(5*RS*)-4-Benzylaminocarbonyl-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-phenylethyl]piperazin-2-one (9): Benzyl isocyanate (39 µL, 0.31 mmol) was added to a solution of **5** [(5*R*)/(5*S*) 3:1, 100 mg, 0.31 mmol] in dichloromethane (25 mL), and the mixture was stirred for 3 h at room temperature. Afterwards, the mixture was diluted with dichloromethane (50 mL), the solution was washed with H_2O (2× 25 mL) and brine (25 mL) and dried with Na_2SO_4, and the solvents were evaporated to dryness. The residue was purified by flash chromatography, with 0–6% MeOH gradient in dichloromethane as mobile phase, to afford the epimeric mixture of ureas **9** [(5*R*)/(5*S*) 3:1] as a foam (123 mg, 86%). HPLC: 18.49 min [(5*R*)-**9**] and 18.89 min [(5*S*)-**9**]. ^{1}H NMR (400 MHz, $CDCl_3$), epimer (5*R*)-**9**: δ = 1.29 (s, 3 H), 2.82 (m, 2 H), 3.45 (m, 2 H), 3.56 (d, *J* = 17.5 Hz, 1 H), 4.08 (d, *J* = 17.5 Hz, 1 H), 4.09 (m, 1 H), 4.42 (m, 2 H), 4.55 (d, *J* = 5.5 Hz, 1 H), 4.92 (d, *J* = 9 Hz, 1 H), 5.28 (m, 1 H), 6.66 (m, 1 H), 7.11–7.33 (m, 10 H) ppm. Epimer (5*S*)-**9**: δ = 1.30 (s, 3 H), 2.75 (m, 1 H), 2.95 (dd, *J* = 5, 14 Hz, 1 H), 3.18 (m, 1 H), 3.58 (m, 1 H), 3.90 (d, *J* = 17 Hz, 1 H), 4.08 (m, 1 H), 4.09 (m, 1 H), 4.42 (m, 2 H), 4.55 (m, 1 H), 4.90 (m, 1 H), 5.36 (m, 1 H), 6.55 (m, 1 H), 7.11–7.33 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$), epimer (5*R*)-**9**: δ = 28.2, 37.6, 41.6, 45.1, 51.0, 51.2, 79.8, 126.4, 127.8, 128.4, 128.6, 128.9, 137.7, 139.0, 155.7, 156.5, 166.4 ppm. Epimer (5*S*)-**9**: δ = 28.2, 37.6, 41.6, 45.1, 51.0, 51.2, 79.6, 126.7, 127.3, 127.4, 127.6, 129.0, 137.0, 138.9, 155.9, 157.2, 166.4 ppm. ES-MS: *m*/*z* = 453.5 [M + 1]$^+$. $C_{25}H_{32}N_4O_4$ (452.55): calcd. C 66.35, H 7.13, N 12.38; found C 66.08, H 6.95, N 12.21.

(5*RS*)-4-Benzyloxycarbonyl-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-phenylethyl]piperazin-2-one (10): Propylene oxide (66 µL, 0.93 mmol) and benzyl chloroformate (135 µL, 0.93 mmol) were added at 0 °C to a solution of **5** [(5*R*)/(5*S*) 3:1, 100 mg, 0.31 mmol] in dichloromethane (25 mL), and the mixture was stirred for 24 h at room temperature. Afterwards, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography, with 0–6% MeOH gradient in dichloromethane as mobile phase, to afford the epimeric mixture **10** [(5*R*)/(5*S*) 3:1] as a foam (127 mg, 90%). HPLC: 20.89 min. ^{1}H NMR (400 MHz, [D_6]-DMSO), epimer (5*R*)-**10**: δ = 1.23 (s, 3 H), 2.58 (m, 2 H), 3.22 (d, *J* = 13 Hz, 1 H), 3.26 (m, 1 H), 3.57 (d, *J* = 18 Hz, 1 H), 3.87 (m, 1 H), 4.08 (d, *J* = 18 Hz, 1 H), 4.20 (m, 1 H), 5.11 (m, 2 H), 6.98 (d, *J* = 9 Hz, 1 H), 7.05–7.27, 7.27–7.46 (2× m, 10 H), 7.98 (m, 1 H) ppm. Epimer (5*S*)-**10**: δ = 1.23 (s, 3 H), 2.62 (m, 2 H), 3.20 (m, 1 H), 3.25 (m, 1 H), 3.60 (m, 1 H), 3.87 (m, 1 H), 4.12 (d, *J* = 18 Hz, 1 H), 4.22 (m, 1 H), 5.11 (m, 2 H), 6.60 (d, *J* = 9 Hz, 1 H), 7.05–7.27, 7.27–7.46 (2× m, 10 H), 7.98 (m, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO), epimer (5*R*)-**10**: δ = 28.2, 36.7, 39.6, 44.0, 50.2, 51.1, 66.7, 77.8, 128.0, 128.4, 129.1, 136.8, 138.7, 154.7, 155.6, 165.7 ppm. Epimer (5*S*)-**10**: δ = 28.2, 36.7, 39.6, 43.7, 50.6, 51.4, 66.0, 77.8, 125.9, 127.7, 127.8, 136.5, 138.5, 154.9, 155.6, 165.7 ppm. ES-MS: *m*/*z* = 454.7 [M + 1]$^+$. $C_{25}H_{31}N_3O_5$ (453.54): calcd. C 66.21, H 6.89, N 9.27; found C 66.30, H 7.04, N 9.37.

(5*RS*)-5-[(1*S*)-1-*tert*-Butoxycarbonylamino-2-phenylethyl]-4-[(9*H*-fluoren-9-yl)methoxycarbonyl]piperazin-2-one (11): Propylene oxide (220 µL, 3.1 mmol) and Fmoc chloride (88 mg, 0.34 mmol) were added at 0 °C to a solution of **5** [(5*R*)/(5*S*) 3:1, 100 mg, 0.31 mmol] in dichloromethane (25 mL), and the mixture was stirred overnight at room temperature. Afterwards, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography, with 0–6% MeOH gradient in dichloromethane as mobile phase, to afford the epimeric mixture of *N*-Fmoc-protected piperazin-2-ones **11** [(5*R*)/(5*S*) 3:1] as a white solid (153 mg, 91%). HPLC: 27.45 min. ^{1}H NMR [400 MHz, $(CD_3)_2CO$], epimer (5*R*)-**11**: δ = 1.28 (s, 3 H), 2.77 (m, 2 H), 3.48 (m, 2 H), 3.60 (d, *J* = 18 Hz, 1 H), 4.11 (m, 1 H), 4.15 (m, 1 H), 4.35 (m, 1 H), 4.38 (m, 1 H), 4.51, 4.57 (2× m, 2 H), 6.13 (d, *J* = 9.5 Hz, 1 H), 7.10 (m, 1 H), 7.11–7.48, 7.63–7.99 (2× m, 13 H) ppm. Epimer (5*S*)-**11**: δ = 1.18 (s, 3 H), 2.74 (m, 2 H), 3.46, 3.65 (2× m, 2 H), 3.80 (d, *J* = 18 Hz, 1 H), 4.01 (m, 1 H), 4.06 (m, 1 H), 4.29 (m, 1 H), 4.35 (m, 1 H), 4.37, 4.65 (2× m, 2 H), 6.03 (d, *J* = 9.5 Hz, 1 H), 7.01 (m, 1 H), 7.11–7.48, 7.63–7.99 (2× m, 13 H) ppm. ^{13}C NMR [100 MHz, $(CD_3)_2CO$], epimer (5*R*)-**11**: δ = 28.5, 38.5, 41.4, 45.5, 48.2, 51.6, 53.2, 68.1, 78.9, 120.7, 126.0, 126.9, 128.0, 128.6, 128.9, 130.1, 139.7, 142.2, 145.0, 155.5, 156.3, 166.2 ppm. Epimer (5*S*)-**11**: δ = 28.2, 38.7, 42.3, 46.3, 48.2, 51.9, 53.6, 68.4, 78.9, 120.7, 126.0, 126.9, 128.0, 128.6, 128.9, 130.1, 139.7, 142.2, 145.1, 155.3, 156.3,

166.6 ppm. ES-MS: *m*/*z* = 564.7 [M + Na]$^+$. $C_{32}H_{35}N_3O_5$ (541.65): calcd. C 70.96, H 6.51, N 7.76; found C 70.78, H 6.63, N 7.68.

(5*RS*)-4-Benzyloxycarbonyl-5-[(1*S*)-1-*tert*-butoxycarbonylamino-2-phenylethyl]-1-(methoxycarbonylmethyl)piperazin-2-one (12): Methyl bromoacetate (24 μL, 0.27 mmol) and sodium hydride (11 mg, 0.44 mmol) were added under argon at 0 °C to a solution of the epimeric mixture of piperazin-2-ones **10** [(5*R*)/(5*S*) 3:1, 100 mg, 0.22 mmol] in THF/DMF (9:1, 5 mL), and the mixture was stirred for 1 h. Afterwards, the mixture was diluted with EtOAc (50 mL) and the reaction was quenched by addition of H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), the combined organic layers were washed with brine (20 mL) and dried with Na_2SO_4, and the solvents were evaporated to dryness. The residue was purified by flash chromatography, with 0–4% MeOH gradient in dichloromethane as mobile phase, to afford the epimeric mixture **12** [(5*R*)/(5*S*) 3:1, 93 mg, 80%] as a foam. HPLC: 23.89 min [(5*R*)-**12**] and 23.66 min [(5*S*)-**12**]. ^{1}H NMR [400 MHz, $(CD_3)_2CO$], epimer (5*R*)-**12**: *δ* = 1.31 (s, 3 H), 2.85 (m, 2 H), 3.58 (dd, *J* = 2, 13 Hz, 1 H), 3.71 (s, 3 H), 3.81 (dd, *J* = 4.5, 13 Hz, 1 H), 3.95 (m, 1 H), 4.14 (m, 1 H), 4.23 (m, 1 H), 4.26 (m, 1 H), 4.40 (m, 1 H), 4.44 (m, 1 H), 5.19 (m, 2 H), 6.28 (d, *J* = 9.5 Hz, 1 H), 7.09–7.51 (m, 10 H) ppm. Epimer (5*S*)-**12**: *δ* = 1.31 (s, 3 H), 2.85 (m, 1 H), 3.16 (t, *J* = 13.5 Hz, 1 H), 3.71 (s, 3 H), 3.73 (m, 1 H), 3.82 (m, 1 H), 3.92 (m, 1 H), 3.95 (m, 1 H), 4.23 (m, 1 H), 4.31 (m, 1 H), 4.40 (m, 1 H), 4.44 (m, 1 H), 5.70 (m, 2 H), 5.85 (d, *J* = 8 Hz, 1 H), 7.09–7.51 (m, 10 H) ppm. ^{13}C NMR [100 MHz, $(CD_3)_2$-CO], epimer (5*R*)-**12**: *δ* = 28.5, 38.3, 46.2, 48.0, 49.0, 52.3, 52.4, 53.2, 67.9, 80.0, 126.9, 129.0, 129.3, 129.9, 137.8, 139.6, 155.3, 156.4, 165.6, 170.7 ppm. Epimer (5*S*)-**12**: *δ* = 28.5, 38.2, 46.0, 48.0, 48.8, 52.2, 52.5, 53.7, 67.9, 80.0, 128.6, 128.8, 128.9, 130.3, 137.8, 139.4, 155.0, 156.4, 165.6, 170.4 ppm. ES-MS: *m*/*z* = 548.7 [M + Na]$^+$. $C_{28}H_{35}N_3O_7$ (525.60): calcd. C 63.98, H 6.71, N 7.99; found C 63.81, H 6.85, N 7.91.

(5*RS*)-5-[(1*S*)-1-*tert*-Butoxycarbonylamino-2-phenylethyl]-1-(methoxycarbonylmethyl)piperazin-2-one Hydrochloride (13): Pd(C) (10 mg) and a solution of HCl in EtOAc (3.4 N, 100 μL, 0.34 mmol) were added to a solution of **12** [(5*R*)/(5*S*) 3:1, 90 mg, 0.17 mmol] in MeOH (5 mL), and the mixture was hydrogenated at 1 atm H_2 and room temperature for 1 h. Afterwards, the reaction mixture was filtered through celite and the solvent was evaporated under reduced pressure. The residue was purified by reversed-phase chromatography (Biotage Snap Cartridge C_{18}, 12 g) with a 0–100% CH_3CN gradient in H_2O as mobile phase. The purified compound was dissolved in CH_3CN/H_2O (1:3, 2 mL) and the solution was lyophilized to obtain **13** [(5*R*)/(5*S*) 3:1] as a lyophilized powder (598 mg, 78%). HPLC: 12.97 min [(5*R*)-**13**] and 13.35 min [(5*S*)-**13**]. ^{1}H NMR (400 MHz, [D$_6$]DMSO), epimer (5*R*)-**13**: *δ* = 1.28 (s, 3 H), 2.67 (dd, *J* = 10.5, 14 Hz, 1 H), 2.80 (dd, *J* = 4.5, 14 Hz, 1 H), 3.60 (m, 1 H), 3.69 (s, 3 H), 3.71 (m, 1 H), 3.72 (m, 1 H), 3.74 (d, *J* = 17 Hz, 1 H), 3.85 (d, *J* = 17 Hz, 1 H), 4.12 (m, 1 H), 4.17 (d, *J* = 17 Hz, 1 H), 4.30 (d, *J* = 17 Hz, 1 H), 7.16 (d, *J* = 9.5 Hz, 1 H), 7.18–7.39 (m, 5 H), 9.58 (m, 2 H) ppm. Epimer (5*S*)-**13**: *δ* = 1.23 (s, 3 H), 2.71 (dd, *J* = 11.5, 14 Hz, 1 H), 2.83 (m, 1 H), 3.60 (m, 1 H), 3.64 (m, 1 H), 3.68 (s, 3 H), 3.71 (m, 1 H), 3.74 (d, *J* = 17 Hz, 1 H), 3.91 (d, *J* = 17 Hz, 1 H), 3.98 (m, 1 H), 4.16 (d, *J* = 17 Hz, 1 H), 4.27 (d, *J* = 17 Hz, 1 H), 6.98 (d, *J* = 9.5 Hz, 1 H), 7.18–7.39 (m, 5 H), 9.58 (m, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO), epimer (5*R*)-**13**: *δ* = 28.2, 36.4, 45.0, 47.8, 51.4, 52.1, 55.0, 78.6, 126.5, 128.3, 129.0, 137.6, 155.8, 162.3, 169.0 ppm. Epimer (5*S*)-**13**: *δ* = 28.1, 35.9, 45.0, 48.5, 50.9, 52.1, 54.9, 78.4, 126.5, 128.1, 129.3, 137.6, 155.5, 162.3, 169.0 ppm. ES-MS: *m*/*z* = 392.6 [M – Cl]$^+$. $C_{20}H_{29}N_3O_5$·HCl: C 56.13, H 7.07, N 9.82; found C 56.32, H 6.96, N 9.71.

(8a*RS*)-(1*S*)-1-Benzyl-3,6-dioxooctahydroimidazo[1,5-*a*]pyrazine (14): The epimeric mixture of piperazin-2-ones **5** [(5*R*)/(5*S*) 3:1, 100 mg, 0.31 mmol] was dissolved in a solution of HCl in EtOAc (3.4 N, 5 mL), and the mixture was stirred at room temperature for 30 min. Afterwards, the solvent was evaporated to dryness, the residue was dissolved in CH_3CN/H_2O (1:3, 2 mL), and the solution was lyophilized. TEA (87 μL, 0.62 mmol) was then added to a solution of the lyophilized powder in dichloromethane (10 mL) and the mixture was stirred for 15 min at 0 °C. Afterwards, TEA (101 μL, 0.73 mmol) followed by triphosgene (36 mg, 0.12 mmol) were added, and the mixture was stirred at 0 °C for 2 h. The solution was diluted with dichloromethane (10 mL), washed with H_2O (2 × 5 mL) and brine (5 mL) and dried with Na_2SO_4, and the solvents were evaporated to dryness. The residue was purified by flash chromatography, with 0–6% MeOH gradient in dichloromethane as mobile phase, to afford the epimeric mixture of imidazopyrazines **14** [(8a*R*)/(8a*S*) 3:1, 46 mg, 60%] as a foam. HPLC: 10.62 min. ^{1}H NMR (400 MHz, [D$_6$]DMSO), epimer (8a*R*)-**14**: *δ* = 2.77 (d, *J* = 7.5 Hz, 2 H), 2.94 (ddd, *J* = 4, 5, 12 Hz, 1 H), 3.37 (t, *J* = 12 Hz, 1 H), 3.43 (d, *J* = 18 Hz, 1 H), 3.72 (ddd, *J* = 5, 7.5, 12 Hz, 1 H), 3.93 (d, *J* = 18 Hz, 1 H), 4.09 (q, *J* = 7.5 Hz, 1 H), 6.79 (m, 1 H), 7.14–7.40 (m, 5 H), 7.95 (d, *J* = 4 Hz, 1 H) ppm. Epimer (8a*S*)-**14**: *δ* = 2.77 (m, 2 H), 2.68 (m, 1 H), 2.85 (dd, *J* = 5, 13 Hz, 1 H), 3.40 (d, *J* = 18 Hz, 1 H), 3.50 (m, 1 H), 3.83 (d, *J* = 18 Hz, 1 H), 4.09 (m, 1 H), 6.94 (m, 1 H), 7.14–7.40 (m, 5 H), 7.84 (d, *J* = 5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO), epimer (8a*R*)-**14**: *δ* = 35.4, 39.8, 44.2, 52.9, 53.3, 127.1, 129.2, 129.4, 138.5, 160.7, 166.9 ppm. Epimer (8a*S*)-**14**: *δ* = 35.4, 44.2, 44.3, 54.6, 55.0, 127.2, 129.1, 130.0, 137.7, 159.7, 167.0 ppm. ES-MS:: *m*/*z* = 246.3 [M + 1]$^+$. $C_{13}H_{15}N_3O_2$ (%):C: 63.66, H: 6.16, N: 17.13; found C: 63.80, H: 6.02, N: 17.28.

General Procedure for the Synthesis of Pyrazino[1,2-*a*]pyrazines: An epimeric mixture of the corresponding 4-(benzyloxycarbonylmethyl)piperazin-2-ones **6** or **8** [(5*R*)/(5*S*) 3:1, 0.17 mmol] was dissolved in a solution of HCl in EtOAc (3.4 N, 5 mL), and the mixture was stirred at room temperature for 30 min. Afterwards, the solvent was evaporated to dryness, the residue was dissolved in CH_3CN/H_2O (1:3, 2 mL), and the solution was lyophilized. TEA (24 μL, 0.68 mmol) was then added to a solution of the lyophilized powder in CH_3CN (5 mL), and the mixture was stirred for 30 min at 100 °C under MW heating conditions. Afterwards, the solvent was evaporated to dryness and the residue was purified by flash chromatography, with a 0–6% MeOH gradient in dichloromethane as mobile phase, to afford the epimeric mixture of pyrazino[1,2-*a*]pyrazines [(9a*R*)/(9a*S*) 3:1] as a foam.

(1*S*,9a*RS*)-1-Benzyl-3,7-dioxooctahydro-1*H*-pyrazino[1,2-*a*]pyrazine (15): (35 mg, 80%). HPLC: 9.08 min **[**(9a*R*)-**15]** and 9.28 min **[**(9a*S*)-**15]**. ^{1}H NMR (400 MHz, $CDCl_3$), epimer (9a*R*)-**15**: *δ* = 2.60 (dd, *J* = 10, 13 Hz, 1 H), 2.76 (dd, *J* = 6, 13 Hz, 1 H), 3.23 (d, *J* = 18 Hz, 1 H), 3.31 (m, 1 H), 3.37 (m, 1 H), 3.43 (d, *J* = 12.5 Hz, 1 H), 3.46 (d, *J* = 12.5 Hz, 1 H), 3.60 (d, *J* = 18 Hz, 1 H), 3.75 (t, *J* = 13 Hz, 1 H), 4.08 (m, 1 H), 6.08 (m, 1 H), 6.87 (m, 1 H), 7.16–7.21, 7.27–7.41 (m, 5 H) ppm. Epimer (9a*S*)-**15**: *δ* = 2.69 (dd, *J* = 9.5, 13.5 Hz, 1 H), 2.83 (m, 1 H), 2.99 (dd, *J* = 7, 13.5 Hz, 1 H), 3.12 (d, *J* = 14.5 Hz, 1 H), 3.16 (d, *J* = 14.5 Hz, 1 H), 3.36 (m, 1 H), 3.46 (m, 2 H), 3.48 (t, *J* = 13 Hz, 1 H), 3.56 (m, 1 H), 6.08 (m, 1 H), 6.94 (m, 1 H), 7.16–7.21, 7.27–7.41 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$), epimer (9a*R*)-**15**: *δ* = 36.5, 37.7, 51.5, 51.7, 54.3, 55.5, 127.6, 128.9, 129.3, 135.2, 168.2, 168.7 ppm. Epimer (9a*S*)-**15**: *δ* = 40.3, 42.7, 54.4, 54.7, 54.8, 55.5, 127.5, 128.9, 129.2, 135.3, 167.6, 168.7. 16.39 ppm.

(1*S*,9a*RS*)-1,8-Dibenzyl-3,7-dioxooctahydro-1*H*-pyrazino[1,2-*a*]pyrazine (16): (41 mg, 85%). HPLC: 15.46 min **[**(9a*R*)-**16]** and

15.69 min [(9a*S*)-**16**]. ^{1}H NMR (400 MHz, $CDCl_3$), epimer (9a*R*)-**16**: δ = 2.48 (dd, J = 10 and 13 Hz, 1 H), 2.70 (dd, J = 6 and 13 Hz, 1 H), 3.16 (dd, J = 5 and 12 Hz, 1 H), 3.37 (m, 1 H), 3.40 (m, 2 H), 3.41 (d, J = 17.5 Hz, 1 H), 3.59 (dd, J = 12 and 14 Hz, 1 H), 3.65 (d, J = 17.5 Hz, 1 H), 3.99 (m, 1 H), 4.51 (d, J = 15 Hz, 1 H), 4.80 (d, J = 15 Hz, 1 H), 5.70 (m, 1 H), 6.99–7.12, 7.19–7.46 (m, 10 H) ppm. Epimer (9a*S*)-**16**: δ = 2.54 (dd, J = 9.5 and 13.5 Hz, 1 H), 2.81 (m, 2 H), 3.11 (d, J = 17 Hz, 1 H), 3.23 (d, J = 17 Hz, 1 H), 3.32 (m, 2 H), 3.36 (d, J = 17 Hz, 1 H), 3.48 (m, 1 H), 3.57 (d, J = 17 Hz, 1 H), 4.54 (d, J = 15 Hz, 1 H), 4.70 (d, J = 15 Hz, 1 H), 5.74 (m, 1 H), 6.99–7.12, 7.19–7.46 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$), epimer (9a*R*)-**16**: δ = 37.7, 40.6, 50.1, 51.6, 52.6, 54.4, 55.9, 127.6, 127.9, 128.1, 128.8, 128.9, 129.2, 135.1, 136.0, 165.6, 167.9 ppm. Epimer (9a*S*)-**16**: δ = 40.2, 47.5, 49.5, 54.4, 54.9, 55.6, 55.8, 127.6, 127.9, 128.2, 128.9, 129.1, 129.2, 135.0, 135.9, 166.5, 167.4 ppm. ES-MS: m/z 350.0 $[M + 1]^+$. $C_{21}H_{23}N_3O_2$ (%):C: 72.18, H: 6.63, N: 12.03; found C: 72.31, H: 6.57, N: 12.14.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra for all new compounds.

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[1] C. De Risi, M. Pelà, G. P. Pollini, C. Trapella, V. Zanirato, *Tetrahedron: Asymmetry* **2010**, *21*, 255–274.
[2] C. Knox, V. Law, T. Jewison, P. Liu, S. Ly, A. Frolkis, A. Pon, K. Banco, C. Mak, V. Neveu, Y. Djoumbou, R. Eisner, A. C. Guo, D. S. Wishart, *Nucleic Acids Res. 39*, D1035–D1041.
[3] Y. Nakao, A. Masuda, S. Matsunaga, N. Fusetani, *J. Am. Chem. Soc.* **1999**, *121*, 2425–2431.
[4] B. M. Trost, N. Cramer, H. Bernsmann, *J. Am. Chem. Soc.* **2007**, *129*, 3086–3087.
[5] C. Wallwey, S.-M. Li, *Nat. Prod. Rep.* **2011**, *28*, 496–510.
[6] T. Hirose, T. Sunazuka, S. Tsuchiya, T. Tanaka, Y. Kojima, R. Mori, M. Iwatsuki, S. Ōmura, *Chem. Eur. J.* **2008**, *14*, 8220–8238.
[7] X. Tian, R. K. Mishra, A. G. Switzer, X. E. Hu, N. Kim, A. W. Mazur, F. H. Ebetino, J. A. Wos, D. Crossdoersen, B. B. Pinney, J. A. Farmer, R. J. Sheldon, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4668–4673.
[8] D. C. Horwell, R. A. Lewthwaite, M. C. Pritchard, G. S. Ratcliffe, J. R. Rubin, *Tetrahedron* **1998**, *54*, 4591–4606.
[9] Y. Zhang, B. P. Gilmour, H. A. Navarro, S. P. Runyon, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4064–4067.
[10] S. Kitamura, H. Fukushi, T. Miyawaki, M. Kawamura, N. Konishi, Z.-i. Terashita, T. Naka, *J. Med. Chem.* **2001**, *44*, 2438–2450.
[11] a) N. A. Powell, E. H. Clay, D. D. Holsworth, J. W. Bryant, M. J. Ryan, M. Jalaie, E. Zhang, J. J. Edmunds, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2371–2374; b) H. Peng, D. Carrico, V. Thai, M. Blaskovich, C. Bucher, E. E. Pusateri, S. M. Sebti, A. D. Hamilton, *Org. Biomol. Chem.* **2006**, *4*, 1768–1784; c) J. N. Cumming, T. X. Le, S. Babu, C. Carroll, X. Chen, L. Favreau, P. Gaspari, T. Guo, D. W. Hobbs, Y. Huang, U. Iserloh, M. E. Kennedy, R. Kuvelkar, G. Li, J. Lowrie, N. A. McHugh, L. Ozgur, J. Pan, E. M. Parker, K. Saionz, A. W. Stamford, C. Strickland, D. Tadesse, J. Voigt, L. Wang, Y. Wu, L. Zhang, Q. Zhang, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3236–3241.
[12] a) S. Herrero, M. T. García-López, M. Latorre, E. Cenarruzabeitia, J. Del Rio, R. Herranz, *J. Org. Chem.* **2002**, *67*, 3866–3873; b) K. Guitot, S. Carboni, O. Reiser, U. Piarulli, *J. Org. Chem.* **2009**, *74*, 8433–8436.
[13] P. Tosovská, P. S. Arora, *Org. Lett.* **2010**, *12*, 1588–1591.
[14] a) A. Pohlmann, V. Schanen, D. Guillaume, J.-C. Quirion, H.-P. Husson, *J. Org. Chem.* **1997**, *62*, 1016–1022; b) A. Viso, R. Fernández de la Pradilla, A. Flores, A. García, M. Tortosa, M. L. López-Rodríguez, *J. Org. Chem.* **2006**, *71*, 1442–1448.
[15] Standard abbreviations for amino acids, peptides, pseudopeptides and protecting groups follow the recommendations of the IUPAC-IUB Joint Commission on Biochemical Nomenclature.
[16] R. Herranz, M. L. Suárez-Gea, S. Vinuesa, M. T. García-López, *J. Org. Chem.* **1993**, *58*, 5186–5191.
[17] S. Herrero, M. L. Suárez-Gea, M. T. García-López, R. Herranz, *Tetrahedron Lett.* **2002**, *43*, 1421–1424.
[18] It should be noted that the priority order of the substituents on the stereogenic center changes after reduction, so the *R* epimer becomes the *S* and vice versa.
[19] A. M. Valdivielso, *Ph.D. dissertation*, **2012**.
[20] J.-A. Fehrentz, B. Castro, *Synthesis* **1983**, 676–678.

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