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Synthesis of enantiopure vicinal diaminoesters and ketopiperazines from *N*-sulfinylimidazolidines

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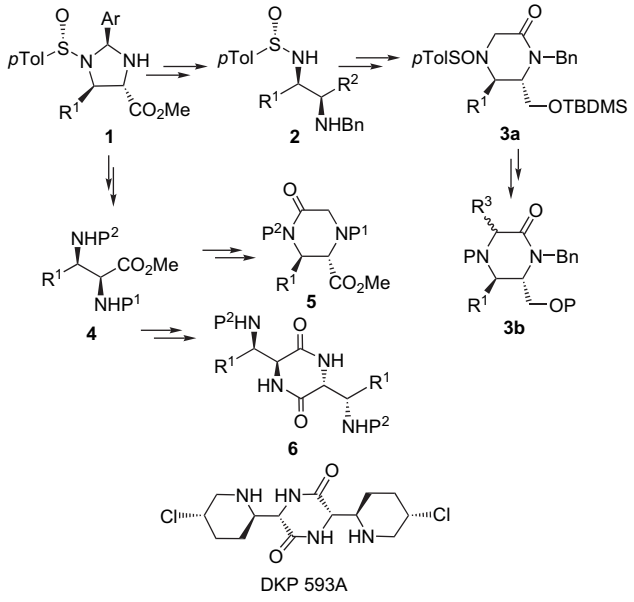
Abstract—A short and efficient synthesis of mono- and bicyclic ketopiperazines bearing methoxycarbonyl substituents is described. The route entails selective protection and solvolysis of *N*-sulfinylimidazolidines to provide vicinal diaminoesters with the nitrogen atoms suitably differentiated. Then, an N-acylation/cyclization protocol renders the ketopiperazines. In addition a diastereoselective route to an analog of the natural diketopiperazine DKP 593A through a 2-piperidinylglycinate available by this method is described.

1. Introduction

Piperazines are a class of structures truly ubiquitous in molecules involved in the regulation of a wide variety of biological processes.[1] The broad range of bioactivities found for these molecules has led to their description as 'privileged structures'. In particular, ketopiperazines have gained importance as conformationally restricted peptidomimetics,[2] as fragments of natural products of diverse structural complexity and biological activities,[3] and also have been examined as ligands in enantioselective catalysis.[4] The increasing interest for these compounds entails the search of efficient routes toward ketopiperazines. In spite of the existing routes to prepare ketopiperazines, the synthesis of highly substituted enantiopure piperazinones is still a challenge especially for compounds that do not derive directly from natural amino acids.

In this context and within a program directed to the discovery of new bioactive piperazine derivatives,[1a] a few years ago our research group developed a process to obtain *N*-sulfinyl-2-piperazinones **3a** from enantiopure imidazolidines (Scheme 1). *N*-Sulfinylimidazolidines **1**, generated from enantiopure *p*-tolylsulfinimines, were submitted to reductive cleavage of the aminal moiety and protection producing *N*-sulfinyldiamines **2**[5a] (R^2=$CH_2OTBDMS$) followed by N-acylation with $ClCH_2COCl$ and cyclization by nucleophilic attack of the sulfinamide onto the chloride. Subsequently, we found that these *N*-sulfinyl-2-piperazinones **3a** were practical intermediates for the diastereoselective synthesis of enantiopure highly substituted piperazinones **3b** [R^3=allyl, alkyl, cyanide, P=H] by nucleophilic addition onto 5,6-dihydropyrazine derivatives generated by elimination of sulfinic acid on **3a**.[5c] Moreover, piperazino-β-lactams (**3b**, R^3=P=–CH(R)–CO–) are easily obtained from these intermediates.[5d] However, this method gave poor yields when *N*-sulfinyldiaminoesters **2** (R^2=CO_2Me), available through selective imidazolidine hydrolysis,[5b] were used as starting materials. Furthermore, more functionalized *N*-sulfinylimidazolidines **1** [R^1=$(CH_2)_4OTs$] could not be submitted to this protocol without losing the tosyloxy group during the aminal reductive cleavage effected with lithium aluminum hydride.[6]



Scheme 1. Routes to ketopiperazines from *N*-sulfinyl-1,3-imidazolidines.

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To overcome the above limitations, we examined a new route compatible with both ester and sulfonate functionalities providing ketopiperazines **5** from *N*-sulfinylimidazolidines **1** through vicinal diaminoesters **4** in which both nitrogen atoms are suitably differentiated. Additionally, we have explored the synthesis of an analog of the natural product DKP 593A that contains a 2,5-diketopiperazine core (**6**).[7] Herein we disclose in full our efforts in pursuing these goals.

2. Results and discussion

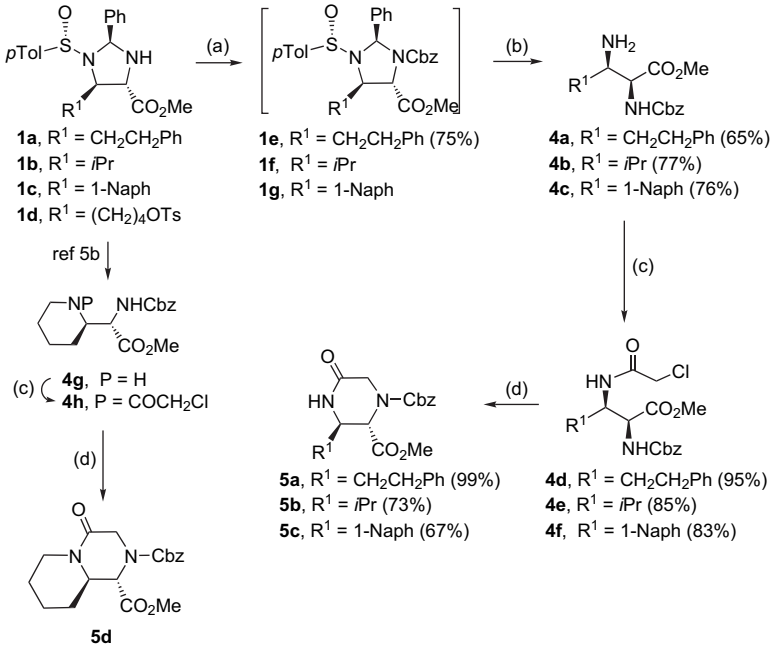
2.1. Preparation of 2-oxopiperazines

The set of *N*-sulfinylimidazolidines **1a–d** chosen for this study was synthesized following the procedure previously reported by us from *p*-tolylsulfinimines and glycine-derived enolates.[5] The synthetic approach to prepare ketopiperazines **5** begins with protection of **1** as benzyloxycarbamate and then simultaneous hydrolysis and desulfinylation with 0.5 M aqueous H_3PO_4 in MeOH (Scheme 2). Initially, we tested these protocols for **1a** (R^1=CH_2CH_2Ph) to afford **1e** and **4a** in good yields (75% and 65%). Under similar conditions, *N*-benzyloxycarbonyl imidazolidine **1f** (R^1=*i*-Pr) was obtained as a single product in the crude mixture, however, after column chromatography **1f** partially decomposed providing finally only 35% yield of diaminoester **4b**. Seeking an improvement in yield of diaminoester **4b**, we avoided purification of *N*-benzyloxycarbonyl imidazolidine **1f** that was directly treated under acidic conditions to afford **4b** in 77% overall yield. Similarly, *N*-sulfinylimidazolidine **1c** (R^1=1-naphthyl) gave raise to **4c** in good yields through *N*-benzyloxycarbonyl imidazolidine **1g**. Once we had prepared diaminoesters **4a–c**, with the nitrogen atoms differentially protected, we carried out a selective N-acylation with $ClCOCH_2Cl$ under mild conditions to give chloroacetamides **4d–f** and then cyclization of the carbamate onto the chloride took place in the presence of Cs_2CO_3 giving 5-oxopiperazino-2-carboxylates **5a–c**. The stereochemistry for **5a–c** was confirmed by the small coupling constants ($J_{2,3}$=1.7–0 Hz) along with NOE experiments that indicate a trans diaxial arrangement of the substituents thus ruling out any epimerization α to the ester (C-2).

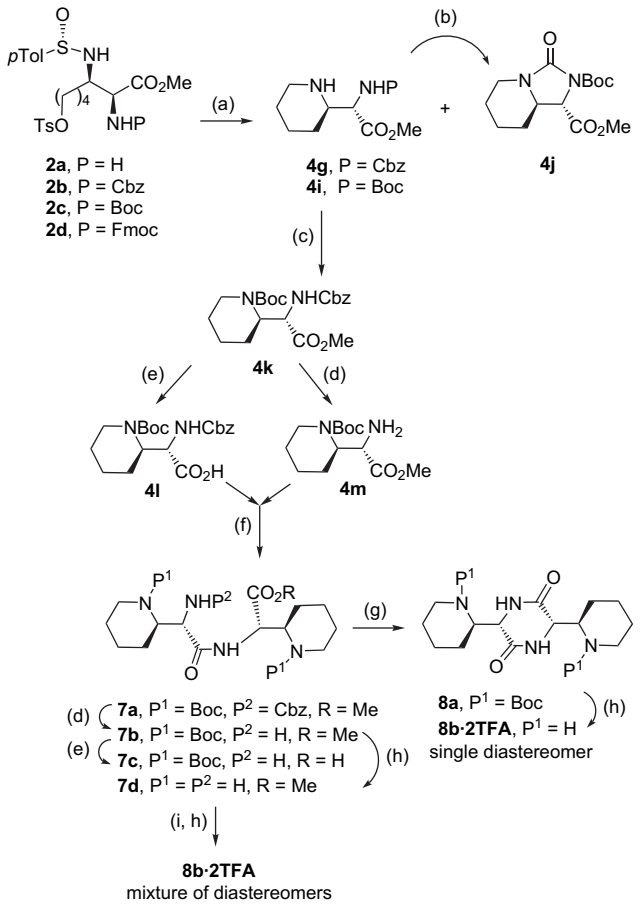
To broaden the scope of this procedure we explored the N-acylation/cyclization protocol for **4g** [R^1=–$(CH_2)_4$–] to afford bicyclic ketopiperazines (Scheme 2). In previous reports, we have demonstrated the efficient formation of methyl 2-piperidinylglycinate **4g** from **1d** by selective aminal solvolysis (H_3PO_4/THF), protection (CbzCl/NaOH), and simultaneous desulfinylation/cyclization (H_3PO_4/MeOH) procedures.[5b] Consequently, 2-piperidinylglycinate **4g** was treated with $ClCH_2COCl$ providing chloroacetamide **4h** (80%) followed by cyclization with Cs_2CO_3 affording **5d** in excellent yield (93%). Remarkably, piperidinylglycinate **4g** is a cyclic α,β-diaminoester related to the antibacterial and antitumor agent DKP 593A isolated from *Streptomyces griseoluteus*.[8] Efficient routes to prepare this natural product and its analogs are scarce and they are often synthesized as racemic and diastereomeric mixtures.[9] Taking these facts into consideration, we focused our attention on the diastereoselective synthesis of **8b** (Scheme 3), the simplest tricyclic analog of DKP 593A from piperidinylglycinate **4g**.

2.2. Synthesis of diketopiperazine 8b·2TFA

At the inception of this study, we considered a strategy consisting of firstly creating the 2,5-diketopiperazine core from *N*-sulfinyldiaminoester **2a**[5b] and secondly effecting a double cyclization of the side chains to form the piperidine rings. Unfortunately, all attempts to carry out this challenging



Scheme 2. Synthesis of 5-oxopiperazino-2-carboxylates from *N*-sulfinyl-1,3-imidazolidines. Reagents and conditions: (a) CbzCl, NaOH 1 N, CH_2Cl_2, 0 °C to rt; (b) H_3PO_4, rt, MeOH/H_2O; (c) $ClCH_2COCl$, 0 °C to rt, 50:50 EtOAc/$NaHCO_3$ satd; (d) Cs_2CO_3, DMF, 62 °C.



Scheme 3. Synthesis of an analog of DKP 593A, **8b**. Reagents and conditions: (a) (i) H_3PO_4, MeOH/H_2O; (ii) K_2CO_3, rt; (b) $(Cl_3CO)_2CO$, CH_2Cl_2, −78 °C; (c) $(Boc)_2O$, NEt_3, dioxane/H_2O, 0 °C to rt; (d) Pd(C), H_2 (45 psi), rt; (e) LiOH, THF/H_2O, 0 °C, rt; (f) BOP, DIPEA, CH_2Cl_2, 0 °C to rt; (g) DMF, reflux, 40 h or KCN, DMF, 80 °C, four days; (h) TFA, CH_2Cl_2, 2 h; (i) NaOH, 0.1 N, rt, 16 days.

route were fruitless and therefore we planned a different approach. Thus, several protecting groups were installed in *N*-sulfinyldiaminoester **2a** to evaluate their behavior in the synthesis of 2-piperidinylglycinates **4** and eventually in the synthesis of **8b** (Scheme 3). Consequently, we prepared carbamate **2c** (P=Boc) from *N*-sulfinyldiaminoester **2a** in 65% yield and subsequent treatment with H_3PO_4 in MeOH followed by addition of solid K_2CO_3 allowed for the isolation of **4i** (60%) and **4j** (17%). Imidazolidinone **4j** was probably formed from **4i** during treatment with K_2CO_3 since performing basic treatment with a solution of NaOH (1 N) prevented formation of **4j** although it provided a lower yield of **4i** (42%). The structural assignment of **4j** was further confirmed by chemical means by submitting **4i** to cyclization with $Cl_3COC(O)OCl_3$ affording **4j** (91%). Similarly, **2d** (P=Fmoc) was obtained from **2a** in moderate yield (41%), however, this carbamate failed in giving the expected *N*-Fmoc piperidinylglycinate. The above results made us choose **4g** as the starting point to address the synthesis of **8b**.

Accordingly, benzyloxycarbamate **4g** was further protected with a Boc group attached to the piperidine nitrogen affording **4k** (82%) that was saponified with LiOH/H_2O to render acid **4l** in excellent yield. At this point chemoselective deprotection of **4k** was also studied. Initial efforts to remove the benzyloxycarbamate group with Pd_2dba_3/$HSiEt_3$[10] and $HSEt/BF_3\cdot OEt_2$[11] produced complete deprotection affording the known methyl 2(*S*)-piperidin-(2′*R*)-yl glycinate thus ruling out any epimerization in our synthetic route.[12] Nevertheless, we found that catalytic hydrogenation afforded amine **4m** in almost quantitative yield. Subsequent coupling of the acid **4l** and the amine **4m** using BOP and DIPEA provided **7a** and further removal of Cbz group afforded **7b** in 85% yield (two steps). At this stage we explored the cyclization of aminoester **7b** and found that refluxing **7b** in solvents such as MeOH, toluene, dioxane, and xylene led to the recovery of starting material even in the presence of Et_3N. After other failed attempts,[13] the diketopiperazine ring was formed in refluxing DMF (22%) or with KCN in DMF at 80 °C (29%). In these two reaction conditions **8a** was obtained with modest yield but as a single isomer that was deprotected with TFA/CH_2Cl_2 and then characterized as **8b·2TFA**. Seeking to improve the cyclization step, we saponified **7b** to afford aminoacid **7c** that was treated under coupling conditions (BOP/DIPEA, HATU/DIPEA) always recovering starting material or complex reaction mixtures.

Alternatively, we envisioned that dipeptide **7d** lacking *N*-piperidine protecting groups could be a suitable substrate for preparing the diketopiperazine nucleus. Therefore, *tert*-butoxycarbamates were uneventfully removed from **7b** with TFA to obtain **7d·3TFA** in high conversion (75%). After some failed experiments,[14] **7d·3TFA** was treated with 0.1 N NaOH monitoring the pH to 8,[15] providing after 16 days diketopiperazine **8b** in 99% yield, but as a mixture of diastereomers, that was finally isolated and characterized as **8b·2TFA**. Controlling the pH proved crucial since a higher base concentration (10% NaOH) produced saponification of the ester group (**7e** not shown) and latter efforts to cyclize the aminoacid were fruitless.

In summary, we have developed an efficient synthesis of enantiopure mono- and bicyclic ketopiperazine-2-carboxylates from *N*-sulfinyl-1,3-imidazolidines. In addition, we have addressed a diastereoselective synthesis of an analog of DKP 593A containing the three main cycles of the structure from an enantiopure 2-piperidinylglycinate available from *N*-sulfinylimidazolidines through the methodology developed in our laboratory.

3. Experimental section

3.1. General procedures

Reagents and solvents were handled by using standard syringe techniques. CH_2Cl_2 was distilled from CaH_2, and THF from sodium. DMF was dried over CaH_2 and filtered before distillation under reduced pressure. Then, it was collected over 4 Å molecular sieves and argon was bubbled through for 10 min before storing it. Crude products were purified by flash chromatography on Merck 230–400 mesh silica gel with distilled solvents. Analytical TLC was carried out on Merck (Kieselgel 60 F_{254}) silica gel plates with detection by UV light, iodine, and 10% phosphomolybdic acid solution in ethanol. Throughout this article, the volume of solvents is reported in mL/mmol of starting material. Infrared spectra (IR) were obtained on a Perkin–Elmer 681 and

on a Perkin–Elmer Spectrum one. ^{1}H and ^{13}C NMR spectra were recorded on a Brüker AM-200 (200 MHz), Varian Gemini-200 (200 MHz), Varian INOVA-300 (300 MHz), and Varian INOVA-400 (400 MHz) using $CDCl_3$ as solvent and with the residual solvent signal as internal reference ($CDCl_3$, 7.24 and 77.0 ppm) unless otherwise noted. NMR signal assignments were based on selective decoupling, HSQC, HMBC, COSY, and NOESY-1D experiments. Melting points were determined on a Reichert Kofler microscope and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20 °C using a sodium lamp and in $CHCl_3$ solution. Low resolution mass spectra in the positive mode were recorded by direct injection on a Hewlett Packard 5973 MSD instrument using the electronic impact technique with an ionization energy of 70 eV or on a Hewlett Packard 1100 MSD instrument using the atmospheric pressure chemical ionization (APCI) or electrospray (ES) chemical ionization techniques in its positive or negative mode. Elemental analyses were carried out on a Perkin–Elmer 240 C and on a Heraus CHN-O-Rapid instruments at Instituto de Química Orgánica, CSIC (Madrid).

3.1.1. General procedure for the synthesis of *N*-benzyloxycarbonyl-α,β-diaminoesters, 4a–c. The synthesis of **4a–c** was performed in two steps avoiding purification of the unstable intermediates **1e–g**, therefore, just partial data of **1e–g** were obtained. *Synthesis of N-benzyloxycarbonylimidazolidines*: to a solution of 1 equiv of *N*-sulfinylimidazolidine **1a–c** in CH_2Cl_2 (10 mL/mmol) at 0 °C was added a solution of 1 N aqueous NaOH (4 mL/mmol) and then 0.9 equiv of CbzCl followed by three consecutive additions of 0.2 equiv every 45 min. The mixture was allowed to warm up to room temperature until disappearance of the starting material (monitored by TLC) and then was diluted with CH_2Cl_2 (10 mL/mmol) and water (10 mL/mmol). The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude products **1e–g** that were used without further purification. *Simultaneous solvolytic cleavage of the aminal moiety and desulfinylation*: 4 equiv of H_3PO_4 (from a 0.5 M aqueous solution) was added to a solution of the above crude in MeOH (18 mL/mmol of **1a–c**). The mixture was stirred from 0 °C to room temperature until disappearance of the starting material, monitored by TLC of aliquots basified with solid $NaHCO_3$. The reaction mixture was diluted with Et_2O (10 mL/mmol) and the layers were separated. The aqueous layer was basified with solid K_2CO_3 to pH=10–11 and then extracted with $CHCl_3$. Then the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product that was purified by column chromatography on silica gel.

3.1.1.1. (−)-Methyl [(2*S*,3*R*)-3-amino-2-(benzyloxycarbonylamino)-5-phenyl]pentanoate, 4a. From **1a** (150 mg, 0.334 mmol) and CbzCl (57 μL) according to the general procedure (25 h) was obtained a crude product (**1e**, 146 mg, 0.251 mmol, 75%). Then, **1e** (40 mg, 0.069 mmol) underwent reaction with H_3PO_4 (23 h) to produce **4a** (16 mg, 0.045 mmol, 65%) after column chromatography (0–1% EtOH/Et_2O) and crystallization as a white solid. The complete characterization of **1e** was carried out with a purified sample (chromatography on silica gel 20–40% Et_2O/hexane). Data for *(+)-methyl [(2S,4R,5S,S_S)-1-benzyloxycarbonyl-2-phenyl-4-(2-phenethyl)-3-(p-tolylsulfinyl)-1,3-imidazolidin-5-yl] carboxylate, **1e***: R_f=0.30 (80% Et_2O/hexane). $[\alpha]_D^{20}$ +18.1 (*c* 1.00). ^{1}H NMR (200 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 2.15–2.31 (m, 1H, H-1′), 2.46–2.71 (m, 2H, H-1′, CH_2Ph), 2.82–2.95 (m, 1H, CH_2Ph), 2.41+2.44 (2s, 3H, Me-Tol), 3.56+3.79 (2s, 3H, CO_2Me), 3.88 (m, 1H, H-5), 4.43 (ap t, 1H, *J*=9.0 Hz, H-4), 4.98–5.21 (m, 2H, OCH_2Ph), 6.12+6.22 (2s, 1H, H-2), 7.04–7.38 (m, 15H, Ar-H), 7.47 (d, 2H, *J*=7.5 Hz, Ar-H), 7.61 (d, 2H, *J*=8.2 Hz, Ar-H). ^{13}C NMR (50 MHz) δ 21.4, 32.0+30.7 (1C), 32.7, 52.6+53.4 (1C), 62.4+63.6 (1C), 65.4, 67.3+67.6 (1C), 73.6, 126.1–129.9 (19CH-Ar), 136.0–142.0 (5C-Ar), 154.0 (CO), 170.7 (CO). IR (KBr): 3030, 2951, 2855, 2246, 1755, 1713, 1603, 1496, 1454, 1403, 1349, 1208, 1095, 1016, 916, 813, 734, 698 cm^{-1}. MS (ES): 1187 $[2M+Na]^+$, 583 $[M+1]^+$ (100%), 445 $[M-(TolSO)+1]^+$. Data for **4a**: R_f=0.28 (0.4% EtOH/Et_2O). Mp: 62–63 °C. $[\alpha]_D^{20}$ −1.3 (*c* 2.00). ^{1}H NMR (300 MHz) δ 1.20 (br s, 2H, NH_2), 1.59 (m, 1H, H-4), 1.75 (m, 1H, H-4), 2.70 (ap t, 2H, *J*=7.9 Hz, H-5), 3.30 (m, 1H, H-3), 3.73 (s, 3H, CO_2Me), 4.40 (d, 1H, *J*=7.7 Hz, H-2), 5.12 (s, 2H, OCH_2Ph), 5.70 (d, 1H, *J*=8.5 Hz, NH–CO), 7.14–7.20 (m, 4H, Ar-H), 7.25–7.33 (m, 6H, Ar-H). ^{13}C NMR (50 MHz) δ 32.5, 36.2, 52.2, 52.4, 57.9, 67.1, 126.0 (2C), 128.1 (3C), 128.4, 128.5 (2C), 128.6 (2C), 136.3, 141.3, 156.6 (N–CO), 172.3 (CO_2Me). IR (KBr): 3321, 3062, 3029, 2951, 2857, 1715, 1659, 1603, 1497, 1454, 1437, 1228, 1086, 1051, 1029, 774, 749, 699 cm^{-1}. MS (ES): 357 $[M+1]^+$ (100%). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.34; H, 6.63; N, 7.95.

3.1.1.2. (−)-Methyl [(2*S*,3*R*)-3-amino-2-(benzyloxycarbonylamino)-4-methyl]pentanoate, 4b. From **1b** (183 mg, 0.474 mmol) and CbzCl (104 μL) according to the general procedure (3 h), a crude product (**1f**) was obtained that underwent reaction with H_3PO_4 (18 h) isolating **4b** (107 mg, 0.364 mmol, 77%) after column chromatography (60–100% Et_2O/hexane) as a colorless oil. Complete characterization of **1f** was carried out with a purified sample. Data for *(+)-methyl [(2S,4R,5S,S_S)-1-benzyloxycarbonyl-2-phenyl-4-(iso-propyl)-3-(p-tolylsulfinyl)-1,3-imidazolidin-5-yl]carboxylate, **1f***: R_f=0.26 (60% Et_2O/hexane). $[\alpha]_D^{20}$ +46.5 (*c* 0.40). ^{1}H NMR (300 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 0.85 (d, 3H, *J*=6.6 Hz, Me *i*-Pr), 0.93 (d, 3H, *J*=6.6 Hz, Me *i*-Pr), 1.24 (m, 1H, CH *i*-Pr), 2.39 (s, 3H, Me-Tol), 3.60+3.84 (2s, 3H, CO_2Me), 3.64–3.80 (m, 1H, H-4), 4.48 (m, 1H, H-5), 4.97–5.13 (m, 2H, OCH_2Ph), 6.03+6.12 (2s, 1H, H-2), 6.87 (m, 1H, Ar-H), 7.18–7.59 (m, 13H, Ar-H). ^{13}C NMR (75 MHz) δ 18.8, 20.4, 21.4, 29.4+29.7 (1C), 52.3+52.7 (1C), 63.3, 67.3+67.6 (1C), 68.9, 75.5+76.0 (1C), 126.0 (2C), 127.2 (2C), 127.4, 127.9 (2C), 128.2, 128.4 (2C), 129.6 (2C), 129.7 (2C), 135.9, 137.2, 140.5+140.3 (1C), 141.7+141.9 (1C), 153.7+153.9 (1C, N–CO), 171.4+171.7 (1C, CO_2Me). IR (film): 3028, 2956, 2869, 1743, 1714, 1494, 1407, 1343, 1212, 1094, 753, 697 cm^{-1}. MS (ES): 521 $[M+1]^+$ (100%), 383 $[M-(pTolSO)+2]^+$. Data for **4b**: R_f=0.17 (Et_2O). $[\alpha]_D^{20}$ −18.2 (*c* 0.55). ^{1}H NMR (300 MHz) δ 0.94 (d, 3H, *J*=6.6 Hz, Me *i*-Pr), 0.97 (d, 3H, *J*=6.6 Hz, Me *i*-Pr), 1.14

(br s, 2H, NH_2), 1.52–1.61 (m, 1H, CH *i*-Pr), 2.90 (dd, 1H, *J*=8.2, 2.3 Hz, H-3), 3.72 (s, 3H, CO_2Me), 4.46 (d, 1H, *J*=8.8 Hz, H-2), 5.10 (s, 2H, OCH_2Ph), 5.75 (d, 1H, *J*=8.3 Hz, NH–CO), 7.33 (m, 5H, Ar-H). ^{13}C NMR (75 MHz) δ 19.1, 19.8, 31.0, 52.4, 56.1, 58.5, 67.0, 128.0 (2C), 128.1, 128.5 (2C), 136.3, 156.5 (N–CO), 173.0 (CO_2Me). IR (film): 3339, 3028, 2959, 2869, 1721, 1499, 1342, 1217, 1046, 697 cm^{-1}. MS (ES): 295 $[M+1]^+$ (100%).

3.1.1.3. (−)-Methyl [(2*S*,3*R*)-3-amino-2-(benzyloxycarbonylamino)-3-(1-naphthyl)]propionate, 4c. From **1c** (90 mg, 0.191 mmol) and CbzCl (42 μL) according to the general procedure (3 h), a crude product (**1g**) was obtained that underwent reaction with H_3PO_4 (27 h) isolating **4c** (55 mg, 0.146 mmol, 77%) after column chromatography (30–50% EtOAc/hexane) as a colorless oil. Partial data for *methyl [(2S,4R,5S,S$_S$)-1-benzyloxycarbonyl-4-(1-naphthyl)-2-phenyl-3-(p-tolylsulfinyl)-1,3-imidazolidin-5-yl]carboxylate,* ***1g***: R_f=0.36 (80% Et_2O/hexane). ^1H NMR (300 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 2.35+2.38 (s, 3H, Me-Tol), 3.48+3.56 (2s, 3H, CO_2Me), 5.05–5.17 (m, 2H, OCH_2Ph), 5.65+5.69 (2d, 1H, *J*=3.1 Hz, H-4), 6.28+6.37 (2s, 1H, H-2). Data for **4c**: R_f=0.26 (80% EtOAc/hexane). $[\alpha]_D^{20}$ −50.0 (*c* 0.05). ^1H NMR (300 MHz) δ 1.58 (br s, 2H, NH_2), 3.82 (s, 3H, CO_2Me), 4.64 (d, 1H, *J*=8.1 Hz, H-2), 4.93 (s, 2H, OCH_2Ph), 5.43 (ap s, 1H, H-3), 6.00 (d, 1H, *J*=8.1 Hz, NH–CO), 7.29–7.59 (m, 8H, Ar-H), 7.64 (d, 1H, *J*=7.3 Hz, Ar-H), 7.77 (d, 1H, *J*=8.1 Hz, Ar-H), 7.87 (d, 1H, *J*=8.5 Hz, Ar-H), 8.10 (d, 1H, *J*=8.1 Hz, Ar-H). ^{13}C NMR (75 MHz) δ 51.2, 52.7, 58.1, 66.8, 122.0, 123.2, 125.1, 125.7, 126.7 (2C), 127.4, 128.0, 128.4 (2C), 129.2 (2C), 130.4, 132.9, 133.8, 136.3, 156.3 (N–CO), 172.1 (CO_2Me). IR (film): 3401, 2949, 2920, 2847, 1700, 1647, 1508, 1467, 1352, 1212, 1053, 775 cm^{-1}. MS (ES): 379 $[M+1]^+$ (100%), 318 $[M-CO_2Me+1]^+$.

3.1.2. General procedure for the synthesis of chloroacetamides 4d–f,h. To a cold (0 °C) suspension of **4a–c**,**g** in EtOAc (10 mL/mmol) and a saturated solution of $NaHCO_3$ (10 mL/mmol) was added 2 equiv of freshly distilled chloroacetylchloride. The mixture was stirred and allowed to warm up to room temperature until disappearance of the starting material (TLC). The layers were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic extracts were washed with a saturated solution of NaCl, dried over Na_2SO_4, and filtered to give, after evaporation of the solvents, a crude product that was purified by chromatography on silica gel to afford the chloroacetamide.

3.1.2.1. (+)-Methyl [(2*S*,3*R*)-2-(benzyloxycarbonylamino)-3-(chloroacetylamino)-5-phenyl]pentanoate, 4d. From **4a** (43 mg, 0.121 mmol) and chloroacetylchloride (19 μL) according to the general procedure (3 h) was obtained chloroacetamide **4d** (50 mg, 0.115 mmol, 95%) after purification by crystallization (Et_2O) as a white solid. Data for **4d**: R_f=0.31 (80% Et_2O/hexane). Mp: 114–116 °C. $[\alpha]_D^{20}$ +69.4 (*c* 1.00). ^1H NMR (300 MHz) δ 1.73–1.86 (m, 1H, H-4), 1.95–2.07 (m, 1H, H-4), 2.63–2.76 (m, 2H, H-5), 3.75 (s, 3H, CO_2Me), 3.95 (s, 2H, CH_2Cl), 4.42 (ddd, 1H, *J*=13.4, 9.4, 5.0 Hz, H-3), 4.53 (m, 1H, H-2), 5.13 (s, 2H, OCH_2Ph), 5.58 (d, 1H, *J*=7.6 Hz, NH–Cbz), 6.52 (d, 1H, *J*=9.3 Hz, CO–NH), 7.15–7.36 (m, 10H, Ar-H). ^{13}C NMR (50 MHz) δ 32.3, 33.5, 42.4, 51.9, 52.9, 56.7, 67.5, 126.2 (2C), 128.3 (3C), 128.4 (3C), 128.6 (2C), 135.9, 140.6, 156.3 (NH–CO_2Bn), 166.0 (CO–NH), 170.7 (CO_2Me). IR (KBr): 3435, 3341, 3314, 3027, 2953, 2851, 1731, 1697, 1644, 1539, 1518, 1453, 1436, 1406, 1353, 1266, 1222, 1160, 1042, 744, 706, 611, 475 cm^{-1}. MS (ES): 455 $[M+Na]^+$, 433 $[M+1]^+$ (100%). Anal. Calcd for $C_{22}H_{25}ClN_2O_5$: C, 61.04; H, 5.82; N, 6.47. Found: C, 60.78; H, 5.49; N, 6.46.

3.1.2.2. (+)-Methyl [(2*S*,3*R*)-2-(benzyloxycarbonylamino)-3-(chloroacetylamino)-4-methyl]pentanoate, 4e. From **4b** (75 mg, 0.255 mmol) and chloroacetylchloride (41 μL) according to the general procedure (4 h) was obtained chloroacetamide **4e** (80 mg, 0.216 mmol, 85%) after purification by crystallization (Et_2O) as a white solid. Data for **4e**: R_f=0.27 (80% Et_2O/hexane). Mp: 139–141 °C. $[\alpha]_D^{20}$ +81.3 (*c* 0.89). ^1H NMR (300 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 0.93 (d, 3H, *J*=6.8 Hz, Me *i*-Pr), 1.07 (d, 3H, *J*=6.3 Hz, Me *i*-Pr), 1.79–1.91 (m, 1H, CH *i*-Pr), 3.72 (s, 3H, CO_2Me), 3.96+3.97 (2s, 2H, CH_2Cl), 4.05 (ddd, 1H, *J*=9.6, 8.3, 3.9 Hz, H-3), 4.60 (dd, 1H, *J*=8.5, 3.9 Hz, H-2), 5.10 (s, 2H, OCH_2Ph), 5.53 (d, 1H, *J*=9.0 Hz, NHCbz), 6.49 (d, 1H, *J*=9.3 Hz, CONH), 7.30–7.36 (m, 5H, Ar-H). ^{13}C NMR (50 MHz) δ 18.4, 19.9, 29.1, 42.5, 52.8, 55.0, 57.6, 67.4, 128.2 (2C), 128.4, 128.6 (2C), 135.9, 156.4 (NH–CO_2Bn), 166.2 (N–CO), 171.4 (CO_2Me). IR (KBr): 3427, 3309, 3057, 2956, 2876, 1727, 1648, 1537, 1434, 1285, 1247, 1160, 1051, 1008, 701 cm^{-1}. MS (ES): 763 $[2M+Na]^+$, 393 $[M+Na]^+$, 373 $[M+3]^+$, 371 $[M+1]^+$ (100%), 327 $[M-(i\text{-}Pr)]^+$.

3.1.2.3. (+)-Methyl [(2*S*,3*R*)-2-(benzyloxycarbonylamino)-3-(chloroacetylamino)-4-(1-naphthyl)]propionate, 4f. From **4c** (50 mg, 0.132 mmol) and chloroacetylchloride (21 μL) according to the general procedure (3 h) was obtained chloroacetamide **4f** (50 mg, 0.110 mmol, 83%) after purification by column chromatography (10–30% EtOAc/hexane) as a white solid. Data for **4f**: R_f=0.22 (40% EtOAc/hexane). Mp: 125–129 °C. $[\alpha]_D^{20}$ +11.4 (*c* 0.14). ^1H NMR (300 MHz) δ 3.54 (s, 3H, CO_2Me), 3.95 (s, 2H, CH_2Cl), 4.98–5.14 (m, 3H, OCH_2Ph, H-2), 5.57 (d, 1H, *J*=8.7 Hz, NH–Cbz), 6.25 (ap t, 1H, *J*=6.0 Hz, H-3), 7.32–7.60 (m, 10H, NH–CO, Ar-H), 7.80–7.87 (m, 2H, Ar-H), 8.11 (d, 1H, *J*=8.1 Hz, Ar-H). ^{13}C NMR (75 MHz) δ 42.5, 51.2, 52.8, 57.9, 67.3, 122.4, 123.8, 125.1 (2C), 126.1 (2C), 127.0, 128.2, 128.3, 128.5, 129.1, 129.3, 130.8, 133.0, 133.9, 135.9, 156.4 (NH–CO_2Bn), 165.9 (N–CO), 170.2 (CO_2Me). IR (KBr): 3467, 2920, 2847, 1743, 1662, 1533, 1432, 1226, 1158, 1046, 775 cm^{-1}. MS (ES): 931 $[2M+Na]^+$, 477 $[M+Na]^+$, 457 $[M+3]^+$, 455 $[M+1]^+$ (100%).

3.1.2.4. (+)-Methyl [(2*S*)-2-(benzyloxycarbonylamino)-3-(*N*-chloroacetylamino)piperidin-(2′*R*)-yl]acetate, 4h. From **4g** (20 mg, 0.065 mmol) and chloroacetylchloride (11 μL) according to the general procedure (21 h) was obtained chloroacetamide **4h** (20 mg, 0.052 mmol, 80%) after purification by column chromatography (30–50% Et_2O/hexane) and crystallization (Et_2O) as a white solid. Data for **4h**: R_f=0.22 (80% Et_2O/hexane). Mp: 95–97 °C. $[\alpha]_D^{20}$ +22.8 (*c* 0.90). ^1H NMR (300 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers)

δ 1.60 (m, 6H, piperidine-H), 3.25 (td, 1H, J=13.9, 2.9 Hz, pip-H-6′$_{ax}$), 3.58 (dd, 1H, J=14.2, 3.7 Hz, pip-H-6′$_{eq}$), 3.74+3.77 (2s, 3H, CO_2Me), 3.89 (s, 2H, CH_2Cl), 4.76 (dd, 1H, J=11.0, 9.0 Hz, H-2), 4.84 (dd, 1H, J=11.0, 4.2 Hz, pip-H-2′), 5.01 (d, 1H, J=12.2 Hz, OCH_2Ph), 5.08 (d, 1H, J=12.2 Hz, OCH_2Ph), 5.47 (d, 1H, J=8.8 Hz, NH–CO), 7.28–7.35 (m, 5H, Ar-H). ^{13}C NMR (75 MHz) δ 18.9, 25.3, 25.6, 41.0, 42.7, 50.2, 52.5, 53.9, 67.0, 128.2 (2C), 128.2, 128.5 (2C), 136.2, 156.0 (NH–CO_2Bn), 167.3 (N–CO), 171.0 (CO_2Me). IR (KBr): 3467, 3231, 3057, 2949, 2862, 1741, 1716, 1639, 1556, 1433, 1311, 1252, 1198, 1022, 754, 699 cm^{-1}. MS (ES): 385 [M+3]$^+$, 383 [M+1]$^+$ (100%). Anal. Calcd for $C_{18}H_{23}ClN_2O_5$: C, 56.47; H, 6.06; N, 7.32. Found: C, 56.71; H, 6.30; N, 7.46.

3.1.3. General procedure for the synthesis of ketopiperazines, 5a–d. A solution of chloroacetamide **4d**–**f**,**h** in DMF (10 mL/mmol) and 1.8 equiv of solid Cs_2CO_3 was stirred at 65 °C until disappearance of the starting material monitored by TLC. The reaction mixture was cooled down to room temperature and diluted with CH_2Cl_2 and H_2O. The layers were separated and the organic phase was washed with cold water and a saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product that was purified by column chromatography.

3.1.3.1. (+)-Methyl [(2*S*,3*R*)-1-benzyloxycarbonyl-5-oxo-3-(2-phenylethyl)piperazin-2-yl]carboxylate, 5a. From **4d** (40 mg, 0.092 mmol) and Cs_2CO_3 (55 mg) according to the general procedure (3 h) was obtained **5a** (36 mg, 0.091 mmol, 99%) after purification by chromatography (20–50% EtOAc/hexane) as a colorless oil. Data for **5a**: R_f=0.24 (60% EtOAc/hexane). $[\alpha]_D^{20}$ +14.3 (c 0.50). ^{1}H NMR (400 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 1.87–1.96 (m, 2H, H-1′), 2.70 (t, 2H, J=7.8 Hz, H-2′), 3.70+3.74 (2s, 3H, CO_2Me), 3.84+3.89 (m, 1H, H-3), 4.05+4.11 (2d, 1H, J=18.6, 19.3 Hz, H-6), 4.30+4.32 (2d, 1H, J=18.6, 19.3 Hz, H-6), 4.83+5.00 (2d, 1H, J=1.4 Hz, H-2), 5.17+5.20 (2s, 2H, OCH_2Ph), 6.23 (br s, 1H, CO–NH), 7.07 (d, 1H, J=6.8 Hz, Ar-H), 7.14 (d, 1H, J=6.8 Hz, Ar-H), 7.20–7.36 (m, 8H, Ar-H). ^{13}C NMR (75 MHz) δ 32.7, 37.7+37.8 (1C), 46.6, 52.9+53.0 (1C), 53.7, 56.1+56.9 (1C), 68.7+68.9 (1C), 127.1 (2C), 128.6 (2C), 129.0, 129.1, 129.3 (2C), 129.4 (2C), 136.4, 140.7, 155.5+156.3 (1C, CO-Cbz), 167.1+167.4 (1C, N–CO), 170.4 (CO_2Me). IR (film): 3423, 2956, 2920, 2847, 1743, 1677, 1436, 1326, 1265, 1021, 799 cm^{-1}. MS (ES): 793 [2M+1]$^+$, 419 [M+Na]$^+$, 397 [M+1]$^+$ (100%).

3.1.3.2. (−)-Methyl [(2*S*,3*R*)-1-benzyloxycarbonyl-3-(*iso*-propyl)-5-oxopiperazin-2-yl]carboxylate, 5b. From **4e** (42 mg, 0.113 mmol) and Cs_2CO_3 (66 mg) according to the general procedure (4 h) was obtained after purification by chromatography (20–40% EtOAc/hexane) **5b** (20 mg, 0.060 mmol, 53%) as a white foam. Data for **5b**: R_f=0.22 (70% EtOAc/hexane). $[\alpha]_D^{20}$ −5.2 (c 0.82). ^{1}H NMR (300 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 0.90+0.97 (2d, 3H, J=6.6 Hz, Me *i*-Pr), 0.99 (d, 3H, J=6.6 Hz, Me *i*-Pr), 1.69–1.80 (m, 1H, CH *i*-Pr), 3.43+3.50 (2ddd, 1H, J=8.7, 4.9, 1.7 Hz, H-3), 3.70+3.74 (2s, 3H, CO_2Me), 4.02+4.09 (2d, 1H, J=19.0, 18.6 Hz, H-6), 4.24+4.25 (2d, 1H, J=19.0, 18.6 Hz, H-6), 4.93+5.08 (2d, 1H, J=1.7 Hz, H-2), 5.15+5.18 (2s, 2H, OCH_2Ph), 6.86 (br s, 1H, CO–NH), 7.34 (m, 5H, Ar-H). ^{1}H NMR (CD_3OD, 300 MHz) δ 1.11+1.17 (2d, 3H, J=6.8 Hz, Me *i*-Pr), 1.17+1.19 (2d, 3H, J=6.8 Hz, Me *i*-Pr), 1.94 (ap hept, 1H, J=6.8 Hz, CH *i*-Pr), 3.62+3.67 (2dd, 1H, J=8.5, 1.3 Hz, H-3), 3.91+3.95 (2s, 3H, CO_2Me), 4.13+4.21 (2d, 1H, J=18.5, 18.1 Hz, H-6), 4.31+4.38 (2d, 1H, J=18.5, 18.1 Hz, H-6), 5.19+5.24 (2d, 1H, J=1.3 Hz, H-2), 5.33–5.44 (m, 2H, OCH_2Ph), 7.51–7.57 (m, 5H, Ar-H). DNOE between H-2 and H-3: 6.0%, H-2 and H (*i*-Pr): 2.6%, H-3 and NH: 5.7%, H-3 and H-2: 5.2%. ^{13}C NMR (75 MHz) δ 18.8, 19.2+19.3 (1C), 32.7+32.9 (1C), 45.7, 53.0, 53.5+54.1 (1C), 58.6+58.7 (1C), 67.9+68.0 (1C), 127.7+128.0 (2C), 128.3+128.4 (1C), 128.6 (2C), 135.7+135.8 (1C), 154.6+155.4 (1C, N–CO_2Bn), 167.0+167.3 (NH–CO), 170.3 (CO_2Me). IR (film): 3427, 2963, 1743, 1667, 1456, 1411, 1320, 1261, 1211, 1110, 1012, 778, 701 cm^{-1}. MS (ES): 691 [2M+Na]$^+$, 669 [2M+1]$^+$, 357 [M+Na]$^+$, 335 [M+1]$^+$ (100%).

3.1.3.3. (−)-Methyl [(2*S*,3*R*)-1-benzyloxycarbonyl-3-(1-naphthyl)-5-oxopiperazin-2-yl]carboxylate, 5c. From **4f** (15 mg, 0.033 mmol) and Cs_2CO_3 (19 mg) according to the general procedure (4 h 30 min) was obtained after purification by chromatography (30–50% EtOAc/hexane) **5c** (8 mg, 0.019 mmol, 57%) as a colorless oil. Data for **5c**: R_f=0.18 (50% EtOAc/hexane). $[\alpha]_D^{20}$ −67.7 (c 0.26). ^{1}H NMR (300 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 3.88+3.91 (2s, 3H, CO_2Me), 4.14+4.23 (2d, 1H, J=18.7 Hz, H-6$_{ax}$), 4.53+4.69 (2d, 1H, J=18.7 Hz, H-6$_{eq}$), 4.60 (m, 1H, OCH_2Ph), 4.97 (m, 1H, OCH_2Ph), 5.27+5.29 (2s, 1H, H-2), 6.01+6.02 (2d, 1H, J=6.0 Hz, H-3), 6.33 (d, 1H, J=7.1 Hz, Ar-H), 6.47 (m, 1H, CO–NH), 6.98 (t, 1H, J=7.7 Hz, Ar-H), 7.09–7.21 (m, 1H, Ar-H), 7.28–7.64 (m, 7H, Ar-H), 7.83 (t, 1H, J=7.9 Hz, Ar-H), 7.90+7.96 (2d, 1H, J=7.6 Hz, Ar-H), 8.03+8.07 (2d, 1H, J=8.6 Hz, Ar-H). DNOE between H-3 and H-2: 6.5%, H-3 and NH: 8.5%, H-3 and ArH-8: 17%, H-2 and H-3: 3.4%, H-2 and ArH-8: 5.1%. ^{13}C NMR (75 MHz) δ 45.4+45.8 (1C), 53.4, 53.6+54.0 (1C), 56.9+57.3 (1C), 67.5+67.9 (1C), 121.3+121.5 (1C), 123.4+123.9 (1C), 125.0+125.3 (1C), 126.2, 126.9, 127.4, 127.7+128.0 (2C), 128.0+128.5 (1C), 129.3+129.4 (2C), 129.5+129.6 (1C), 133.7, 134.0, 135.2, 135.6, 154.2+155.2 (1C, N–CO_2Bn), 167.4+167.6 (1C, NH–CO), 169.2+169.9 (1C, CO_2Me). IR (film): 3459, 2949, 1747, 1707, 1679, 1418, 1411, 1317, 1268, 1212, 1010, 779, 699 cm^{-1}. MS (ES): 859 [2M+Na]$^+$, 837 [2M+1]$^+$, 441 [M+Na]$^+$, 419 [M+1]$^+$ (100%).

3.1.3.4. (−)-Methyl [(1*S*,8a*R*)-2-(benzyloxycarbonyl)-4-oxoperhydropyrido[1,2-*a*]piperazin-1-yl]carboxylate, 5d. From **4h** (30 mg, 0.078 mmol) and Cs_2CO_3 (46 mg) according to the general procedure (4 h 30 min) was obtained **5d** (25 mg, 0.072 mmol, 93%) as a colorless oil after purification by chromatography (20–50% Et_2O/hexane). Data for **5d**: R_f=0.13 (80% Et_2O/hexane). $[\alpha]_D^{20}$ −6.3 (c 0.91). ^{1}H NMR (300 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 1.41–1.97 (m, 6H, pip-H), 2.53 (ap t, 1H, J=12.7 Hz, H-5$_{ax}$), 3.71+3.75 (2s, 3H, CO_2Me), 3.88+3.93 (2d, 1H, J=15.0 Hz, H-8a), 3.93+3.98 (2d, 1H, J=16.5 Hz, H-3$_{ax}$), 4.39+4.44 (2d, 1H, J=16.5 Hz, H-3$_{eq}$), 4.64 (br d, 1H,

J=12.7 Hz, H-5$_{eq}$), 4.69+4.82 (2 br s, 1H, H-1), 5.18 (s, 2H, OCH_2Ph), 7.35 (m, 5H, Ar-H). ^{13}C NMR (75 MHz) δ 24.6, 24.9, 31.7, 44.8, 45.5+45.6 (1C), 53.0, 56.4+57.2 (1C), 57.7, 68.1, 127.9 (2C), 128.3, 128.6 (2C), 135.7, 155.8 (NH–CO_2Bn), 163.2+163.5 (1C, N–CO), 169.6 (CO_2Me). IR (film): 2925, 2854, 1744, 1711, 1651, 1432, 1325, 1261, 1230, 1126, 1074, 1003, 955, 915, 752, 698, 504 cm^{-1}. MS (ES): 369 [M+Na]$^+$, 347 [M+1]$^+$ (100%).

3.1.4. Synthesis of (+)-methyl [(2*S*,3*R*,S_S)-2-(*tert*-butoxycarbonylamino)-3-(*p*-tolylsulfinylamino)-7-(*p*-tolylsulfonyloxy)]heptanoate, 2c. To a solution of **2a** (46 mg, 0.095 mmol) in CH_2Cl_2 (2 mL) at 0 °C, was added 1 N NaOH (2 mL/mmol) and 1.1 equiv of Boc_2O (23 mg, 0.105 mmol) in CH_2Cl_2 (0.2 mL). The mixture was allowed to warm up to room temperature until total disappearance of the starting material (4 h) monitored by TLC. The mixture was partitioned with H_2O (5 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product that was purified by column chromatography (30–40% EtOAc/hexane). Compound **2c** (36 mg, 0.062 mmol, 65%) was obtained as a colorless oil. Data for **2c**: R_f=0.32 (60% EtOAc/hexane). $[\alpha]_D^{20}$ +70.5 (*c* 1.02). ^1H NMR (400 MHz) δ 1.42 (s, 9H, *t*-Bu Boc), 1.44–1.62 (m, 6H, H-6, H-5, H-4), 2.39 (s, 3H, Me-Tol), 2.42 (s, 3H, Me-Ts), 3.77 (s, 3H, CO_2Me), 3.77 (m, 1H, H-3), 3.92 (d, 1H, J=7.5 Hz, S–NH), 3.97 (m, 2H, H-7), 4.39 (br d, 1H, J=7.0 Hz, H-2), 5.46 (d, 1H, J=8.6 Hz, NH–CO), 7.28 (d, 2H, J=8.1 Hz, Ar-H), 7.32 (d, 2H, J=8.1 Hz, Ar-H), 7.50 (d, 2H, J=8.2 Hz, Ar-H), 7.76 (d, 2H, J=8.2 Hz, Ar-H). ^{13}C NMR (75 MHz) δ 21.3, 21.6, 26.9, 28.2 (3C, Me *t*-Bu Boc), 28.4, 32.5, 52.7, 57.0 (2C), 70.1, 80.3, 125.5 (2C), 127.9 (2C), 129.6 (2C), 129.9 (2C), 133.1, 141.5, 141.7, 144.7, 155.9 (N–CO_2*t*-Bu), 171.5 (CO). IR (film): 3289, 2927, 2855, 1743, 1710, 1523, 1450, 1364, 1208, 1175, 1049, 1010, 811 cm^{-1}. MS (ES): 1187 [2M+Na]$^+$, 605 [M+Na]$^+$, 583 [M+1]$^+$, 445 [M−(*p*TolSO)+2]$^+$ (100%), 273 [M−(*p*TolSO)−OTs+1]$^+$.

3.1.5. Synthesis of methyl [(2*S*,3*R*,S_S)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(*p*-tolylsulfinylamino)-7-(*p*-tolylsulfonyloxy)]heptanoate, 2d. To a solution of **2a** (74 mg, 0.153 mmol) in dioxane was added a solution of 10% aqueous Na_2CO_3 (0.46 mL) and 1.0 equiv of FmocCl (40 mg, 0.153 mmol) at 0 °C. The mixture was stirred at room temperature until disappearance of the starting material monitored by TLC (4 h). Then it was diluted with H_2O (5 mL) and the aqueous layer was extracted with Et_2O (5 mL), brought to pH=2 with 0.5 M aqueous H_3PO_4, and extracted with EtOAc (2×5 mL). The organic extracts were washed with H_2O, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield after purification by chromatography (20–40% EtOAc/hexane) **2d** (44 mg, 0.063 mmol, 41%) as a colorless oil. Partial data for **2d**: R_f=0.24 (50% EtOAc/hexane). ^1H NMR (300 MHz) δ 1.41–1.59 (m, 6H, H-6, H-5, H-4), 2.40 (s, 6H, Me-Tol, Me-Ts), 3.78 (s, 3H, CO_2Me), 3.78 (m, 1H, H-3), 3.97 (m, 2H, H-7), 4.04 (m, 1H, S–NH), 4.22 (t, 1H, J=7.2 Hz, NH–Fmoc), 4.41 (m, 3H, H-2, CH_2-Fmoc), 6.04 (d, 1H, J=8.4 Hz, NH–CO), 7.28–7.32 (m, 6H, Ar-H), 7.37 (td, 2H, J=7.3, 3.7 Hz, Ar-H), 7.53 (d, 2H, J=7.9 Hz, Ar-H), 7.61 (t, 2H, J=8.4 Hz, Ar-H), 7.73 (dd, 2H, J=7.5, 4.4 Hz, Ar-H), 7.76 (d, 2H, J=8.4 Hz, Ar-H).

3.1.6. Synthesis of methyl (2*S*)-[2-(*tert*-butoxycarbonylamino)-2-piperidin-(2′*R*)-yl]acetate, 4i. Compound **2c** (46 mg, 0.079 mmol) in MeOH (1.5 mL) was treated with a 0.5 M solution of aqueous H_3PO_4 (0.63 mL, 0.316 mmol) according to the procedure for the simultaneous solvolytic cleavage of the aminal moiety and desulfinylation (21 h). Then, the mixture was basified with solid K_2CO_3 (45 min at 0 °C) isolating after chromatography (5–20% EtOH/Et_2O) **4i** (13 mg, 0.048 mmol, 60%) as a white foam and **4j** (4 mg, 0.013 mmol, 17%) as a white solid. Alternatively when 1 N NaOH was used (0 °C, 1 h 30 min), **4i** (10 mg, 0.037 mmol, 42%) was produced as a single product after purification. Data for **4i**: R_f=0.22 (20% EtOH/Et_2O). ^1H NMR (300 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 1.30–1.45 (m, 12H, 3H, pip-H, 9H, *t*-Bu Boc), 1.60 (m, 2H, pip-H), 1.78 (m, 1H, pip-H), 2.62 (ap t, 1H, J=11.6 Hz, pip-H-6′$_{ax}$), 3.12 (m, 2H, pip-H-2′, pip-H-6′$_{eq}$), 3.76 (s, 3H, CO_2Me), 4.24 (ap d, 1H, J=5.5 Hz, H-2), 5.82 (d, 1H, J=6.8 Hz, NH–CO). ^{13}C NMR (50 MHz) δ 23.8, 24.9, 28.3 (3C), 28.7, 46.4, 52.6, 57.4 (2C), 79.9, 156.1 (N–CO_2*t*-Bu), 172.2 (CO_2Me). MS (ES): 295 [M+Na]$^+$, 273 [M+1]$^+$ (100%).

3.1.7. Synthesis of (−)-2-(*tert*-butyl)-1-methyl (1*S*,8a*R*)-3-oxohexahydroimidazo[1,5-*a*]pyridin-1,2-(3*H*)dicarboxylate, 4j. To a solution of 0.3 equiv of $Cl_3COC(O)OCCl_3$ (1 mg, 0.004 mmol) in CH_2Cl_2 (0.5 mL) at −78 °C was added a solution of 1.0 equiv of **4i** (4 mg, 0.015 mmol) and 3.0 equiv of NEt_3 (6 μL, 0.044 mmol) in CH_2Cl_2 (2 mL). The mixture was allowed to warm up to room temperature (2 h, monitored by TLC) and then was washed with saturated solution of NaCl (2 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude that was purified by column chromatography (40–50% EtOAc/hexane) to isolate **4j** (4 mg, 0.013 mmol, 91%) as a white solid. Data for **4j**: R_f=0.24 (60% EtOAc/hexane). $[\alpha]_D^{20}$ −28.6 (*c* 0.36). ^1H NMR (300 MHz) δ 1.41 (m, 3H, pip-H), 1.48 (s, 9H, *t*-Bu Boc), 1.61 (m, 1H, pip-H), 1.90 (m, 2H, pip-H), 2.71 (td, 1H, J=12.5, 3.7 Hz, H-5$_{ax}$), 3.38 (dt, 2H, J=10.8, 3.7 Hz, H-5$_{eq}$), 3.76 (s, 3H, CO_2Me), 3.98 (ap dd, 1H, J=13.5, 4.2 Hz, H-8a), 4.18 (d, 1H, J=4.1 Hz, H-1). ^{13}C NMR (75 MHz) δ 23.2, 24.3, 28.0 (3C, Me *t*-Bu Boc), 31.6, 41.0, 52.7, 55.1, 60.0, 82.9, 150.2 (N–CO–N), 151.8 (N–CO_2*t*-Bu), 170.3 (CO_2Me). IR (KBr): 2920, 2847, 2572, 2000, 1747, 1707, 1447, 1367, 1150, 858 cm^{-1}. MS (ES): 619 [2M+Na]$^+$, 321 [M+Na]$^+$ (100%).

3.1.8. Synthesis of (+)-methyl (2*S*)-[2-(benzyloxycarbonylamino)-2-(*N*-*tert*-butoxycarbonyl)piperidin-(2′*R*)-yl]acetate, 4k. To a solution of **4g** (480 mg, 1.569 mmol) in dioxane/H_2O 1:1 (10 mL/mmol) at 0 °C were added 1.2 equiv of NEt_3 (0.26 mL, 1.882 mmol) and 1.1 equiv of a solution of Boc_2O 1 M (376 mg, 1.73 mL, 1.725 mmol) in THF. The mixture was allowed to warm up to room temperature until disappearance of the starting material (15 h) monitored by TLC and then the organic layer was concentrated under reduced pressure. The aqueous phase was extracted with $CHCl_3$ and the combined organic extracts were washed with a saturated solution of NaCl, dried over

Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product that was purified by column chromatography (10–20% Et_2O/hexane) to obtain **4k** (522 mg, 1.286 mmol, 82%) as a colorless oil. Data for **4k**: R_f=0.14 (40% Et_2O/hexane). $[\alpha]_D^{20}$ +9.9 (*c* 0.89). ^1H NMR (300 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 1.41 (m, 9H, *t*-Bu Boc), 1.45–1.65 (m, 6H, pip-H), 2.80 (t, 1H, *J*=12.5 Hz, pip-H-6′$_{ax}$), 3.73 (s, 3H, CO_2Me), 3.95 (m, 1H, pip-H-6′$_{eq}$), 4.45 (m, 1H, pip-H-2′), 4.68+4.72 (2d, 1H, *J*=9.0 Hz, H-2), 5.06 (s, 2H, OCH_2Ph), 5.73 (m, 1H, NH–CO), 7.25–7.34 (m, 5H, Ar-H). ^{13}C NMR (50 MHz) δ 18.9, 24.8, 25.7, 28.2 (3C), 40.0, 50.9, 52.3, 54.1, 66.8, 80.2, 127.8 (2C), 127.9, 128.3 (2C), 136.2, 155.9 (N–CO_2*t*-Bu), 155.9 (NH–CO_2Bn), 171.7 (CO_2Me). IR (film): 3362, 2934, 2862, 1726, 1682, 1515, 1493, 1457, 1413, 1366, 1309, 1272, 1172, 1042, 873, 699 cm^{-1}. MS (ES): 832 $[2M+Na]^+$, 429 $[M+Na]^+$ (100%), 307 $[M-Boc+2]^+$.

3.1.9. Synthesis of (+)-(2*S*)-[2-(benzyloxycarbonylamino)-2-(*N*-*tert*-butoxycarbonyl)piperidin-(2′*R*)-yl]acetic acid, 4l. To a solution of **4k** (224 mg, 0.552 mmol) in THF/H_2O 1:1 (10 mL/mmol) at 0 °C was added 1.2 equiv of LiOH/H_2O (46 mg, 1.103 mmol). The reaction mixture was stirred from 0 °C to room temperature (15 h) and disappearance of the starting material was monitored by TLC. The organic layer was evaporated under reduced pressure and the aqueous phase was washed with CH_2Cl_2, brought to pH=2–3 with 0.5 M H_3PO_4 solution, and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure to produce **4l** (216 mg, 0.550 mmol, 100%) as white foam that was used without further purification. Data for **4l**: $[\alpha]_D^{20}$ +14.3 (*c* 0.44). ^1H NMR (500 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 1.39 (s, 9H, *t*-Bu Boc), 1.62 (m, 5H, pip-H), 1.80 (m, 1H, pip-H), 2.80 (t, 1H, *J*=12.7 Hz, pip-H-6′$_{ax}$), 3.94 (br d, 1H, *J*=12.2 Hz, pip-H-6′$_{eq}$), 4.42 (br d, 1H, *J*=7.8 Hz, pip-H-2′), 4.68+4.70 (2d, 1H, *J*=9.8 Hz, H-2), 5.07 (m, 2H, OCH_2Ph), 5.60+5.75 (2 br s, 1H, NH–CO), 6.94 (br s, CO_2H), 7.29 (m, 5H, Ar-H). ^{13}C NMR (125 MHz) δ 19.0, 24.8, 25.8, 28.3 (3C), 39.9, 51.3, 54.0, 67.0, 80.6, 127.9 (2C), 128.0, 128.4 (2C), 136.1, 156.2 (N–CO_2*t*-Bu), 156.2 (NH–CO_2Bn), 175.2 (CO_2H). IR (film): 3304, 2929, 2855, 1724, 1687, 1515, 1415, 1270, 1161, 1042 cm^{-1}. MS (ES): 807 $[2M+Na]^+$, 415 $[M+Na]^+$ (100%).

3.1.10. Synthesis of (+)-methyl (2*S*)-[2-amino-2-(*N*-*tert*-butoxycarbonyl)piperidin-(2′*R*)-yl]acetate, 4m. To a solution of **4k** (283 mg, 0.697 mmol) in MeOH/H_2O 5:1 (35 mL) was added Pd–C 10% (52 mg) and was hydrogenated at 45 psi monitoring the reaction by TLC (4 h 30 min). The mixture was filtered through Celite and the solvents were evaporated under reduced pressure to give a crude product that was purified by column chromatography (0–4% EtOH/Et_2O) to afford **4m** (189 mg, 0.693 mmol, 100%) as a colorless oil. Data for **4m**: R_f=0.22 (4% EtOH/Et_2O). $[\alpha]_D^{20}$ +2.2 (*c* 0.36). ^1H NMR (CD_3OD, 400 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 1.47 (m, 1H, pip-H), 1.51 (s, 9H, *t*-Bu Boc), 1.65 (m, 5H, pip-H), 2.86 (m, 1H, H-6′$_{ax}$), 3.79 (s, 3H, CO_2Me), 3.86 (d, 1H, *J*=10.6 Hz, H-2), 4.05 (br d, 1H, *J*=13.2 Hz, H-6′$_{eq}$), 4.32 (m, 1H, H-2′). ^{13}C NMR (CD_3OD, 75 MHz) δ 20.4, 26.3, 27.3, 28.8 (3C), 40.1+41.2 (1C), 52.7, 54.9 (2C), 81.6, 157.7 (N–CO_2*t*-Bu), 176.2 (CO_2Me). IR (film): 3400, 2935, 2862, 1739, 1714, 1692, 1414, 1368, 1270, 1162, 1060 cm^{-1}. MS (ES): 295 $[M+Na]^+$, 273 $[M+1]^+$ (100%), 217 $[M-t\text{-Bu}+2]^+$.

3.1.11. Peptide coupling. (+)-*tert*-Butyl (2*R*)-2-[(1*S*)-1-({(2*S*)-2-(benzyloxycarbonyl)amino-2-[1-(*tert*-butoxycarbonyl)piperidin-(2*R*)-yl]acetyl}amino)-2-methoxy-2-oxoethyl]piperidin-1-yl carboxylate, 7a. To a solution of 1 equiv of acid **4l** (216 mg, 0.550 mmol) and 1 equiv of amine **4m** (150 mg, 0.550 mmol) in CH_2Cl_2 (8 mL/mmol) at 0 °C, was added 1.2 equiv of a solution of BOP (292 mg, 0.660 mmol) in CH_2Cl_2 (1.2 mL/mmol) and 2.5 equiv of DIPEA (0.24 mL, 1.376 mmol). The reaction mixture was allowed to warm up to room temperature (monitored by TLC) and then it was diluted with EtOAc (10 mL). The organic phase was washed with a 0.5 M solution of H_3PO_4, with saturated solution of $NaHCO_3$ and with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (20–30% EtOAc/hexane) to give **7a** (347 mg, 0.537 mmol, 98%) as a white foam. Data for **7a**: R_f=0.24 (40% EtOAc/hexane). $[\alpha]_D^{20}$ +10.0 (*c* 0.30). ^1H NMR (300 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 1.38 (s, 9H, *t*-Bu Boc), 1.45 (s, 9H, *t*-Bu Boc), 1.45–1.65 (m, 11H, pip-H), 1.79 (m, 1H, pip-H), 2.79 (m, 2H, pip-H-6$_{ax}$, pip-H-6″$_{ax}$), 3.69+3.70 (2s, 3H, OMe), 3.93 (m, 2H, pip-H-6$_{eq}$, pip-H-6″$_{eq}$), 4.42 (m, 3H, pip-H-2″, pip-H-2, C*H*NHCbz), 4.76 (m, 1H, H-1′), 5.03 (m, 2H, OCH_2Ph), 5.37+5.61 (2 br s, 1H, NH–CO_2Bn), 7.28 (m, 5H, Ar-H). ^1H NMR (CD_3OD, 300 MHz) δ 1.44 (s, 9H, *t*-Bu Boc), 1.46 (s, 9H, *t*-Bu Boc), 1.56–1.83 (m, 12H, pip-H), 2.97 (m, 2H, pip-H-6$_{ax}$, pip-H-6″$_{ax}$), 3.78 (s, 3H, OMe), 3.98 (m, 2H, pip-H-6$_{eq}$, pip-H-6″$_{eq}$), 4.40 (m, 1H, pip-H-2″), 4.51 (m, 1H, pip-H-2), 4.67+4.71 (2d, 1H, *J*=10.0 Hz, C*H*NHCbz), 5.07 (m, 3H, H-1′, OCH_2Ph), 6.54 (br s, 1H, NH–CO_2Bn), 7.36 (m, 5H, Ar-H), 8.55 (s, 1H, NH–CO). ^{13}C NMR (50 MHz) δ 19.1, 19.3, 24.8, 25.0, 25.5, 26.0, 28.3 (6C), 39.8, 40.2, 51.0, 51.7, 52.3, 53.5, 54.4, 66.7+66.9 (1C), 80.1, 80.7, 127.8 (2C), 127.9, 128.3 (2C), 136.2+136.3 (1C), 155.7 (2C, N–CO_2*t*-Bu), 156.2 (NH–CO_2Bn), 170.7 (CO–NH), 171.1 (CO_2Me). IR (KBr): 3333, 2936, 2862, 1740, 1690, 1515, 1416, 1366, 1311, 1273, 1039, 890, 755 cm^{-1}. MS (ES): 1316 $[2M+Na]^+$, 669 $[M+Na]^+$, 217 $[M-CO_2t\text{-Bu}+2]^+$ (100%).

3.1.12. Synthesis of (+)-*tert*-butyl (2*R*)-2-[(1*S*)-1-({(2*S*)-2-amino-2-[1-(*tert*-butoxycarbonyl)piperidin-(2*R*)-yl]-acetyl}amino)-2-methoxy-2-oxoethyl]piperidin-1-yl carboxylate, 7b. From **7a** (83 mg, 0.128 mmol) in MeOH/H_2O 5:1 (5 mL) and Pd–C 10% (10 mg) according to the procedure described for **4l** (4 h) was isolated **7b** (57 mg, 0.111 mmol, 87%) as a white solid after purification by column chromatography (70% EtOAc/CH_2Cl_2). Data for **7b**: R_f=0.24 (EtOAc). Mp: 134–137 °C. $[\alpha]_D^{20}$ +60.2 (*c* 0.13). ^1H NMR (300 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 1.46 (s, 9H, *t*-Bu Boc), 1.48 (s, 9H, *t*-Bu Boc), 1.57–1.64 (m, 11H, pip-H), 1.88 (m, 1H, pip-H), 2.70 (m, 2H, pip-H-6$_{ax}$, H-6″$_{ax}$), 3.63 (m, 1H, C*H*NH_2), 3.73+3.74 (2s, 3H, OMe), 4.02 (m, 2H, pip-H-6$_{eq}$, pip-H-6″$_{eq}$), 4.14 (m, 1H, pip-H-2″), 4.52 (m, 1H, pip-H-2), 4.80+4.82 (2d, 1H,

J=7.7 Hz, H-1′), 7.74 (br s, 1H, NH–CO). ^{1}H NMR (CD_3OD, 400 MHz) δ 1.51 (s, 9H, Me *t*-Bu Boc), 1.53 (s, 9H, Me *t*-Bu Boc), 1.63–1.73 (m, 12H, pip-H), 2.88 (m, 2H, pip-H-6$_{ax}$, pip-H-6″$_{ax}$), 3.72 (d, 1H, J=10.3 Hz, C*H*NH_2), 3.79 (s, 3H, OMe), 4.02 (ap t, 2H, J=15.1 Hz, pip-H-6$_{eq}$, pip-H-6″$_{eq}$), 4.24 (m, 1H, pip-H-2″), 4.52 (m, 1H, pip-H-2), 4.98 (d, 1H, J=10.6 Hz, H-1′). ^{13}C NMR (75 MHz) δ 19.1, 19.5, 24.8, 25.0, 25.5, 26.0, 28.4 (6C), 39.7, 40.2, 50.9 (2C), 52.3+52.4 (1C), 53.3, 54.0, 80.1+80.3 (1C), 80.5+80.6 (1C), 156.0 (N–CO_2*t*-Bu), 156.7 (N–CO_2*t*-Bu), 171.1 (CO–NH), 171.3 (CO_2Me). IR (KBr): 3340, 2935, 2862, 1745, 1689, 1416, 1366, 1310, 1274, 1163, 1038, 869, 755 cm^{-1}. MS (ES): 1025 [2M+1]$^+$, 535 [M+Na]$^+$, 513 [M+1]$^+$ (100%). Anal. Calcd for $C_{25}H_{44}N_4O_7$: C, 58.57; H, 8.65; N, 10.93. Found: C, 58.69; H, 8.79; N, 10.64.

3.1.13. Synthesis of (+)-(2*R*)-2-{(1*S*)-1-ammonium-2-[{(1*S*)-2-methoxy-2-oxo-1-[piperidinium-(2*R*)-yl]ethyl}-amino]-2-oxoethyl}piperidinium tris(trifluoroacetate), 7d·3TFA. *N*-Boc **7b** (52 mg, 0.102 mmol) was dissolved in a mixture of CH_2Cl_2/TFA 1:1 (10 mL/mmol) and was stirred at 0 °C (2 h). The solvent was evaporated under reduced pressure and the residue was redissolved in toluene and concentrated (three times) to remove the excess of TFA. Crystallization (Et_2O) of this crude afforded **7d·3TFA** (50 mg, 0.076 mmol, 75%) as white solid. Data for **7d**: $[\alpha]_D^{20}$ +4.5 (*c* 0.22, MeOH). Mp: 90–92 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.60–1.82 (m, 6H, pip-H), 1.85–2.02 (m, 6H, pip-H), 3.09 (m, 2H, pip-H-6$_{ax}$, pip-H-6″$_{ax}$), 3.49 (m, 3H, pip-H-6$_{eq}$, pip-H-6″$_{eq}$, pip-H-2″), 3.64 (m, 1H, pip-H-2), 3.87 (s, 3H, OMe), 4.00 (d, 1H, J=6.8 Hz, C*H*NH_3), 4.94 (m, 1H, H-1′). ^{13}C NMR (CD_3OD, 75 MHz) δ 21.1 (2C), 21.2, 21.4, 24.7, 24.9, 45.0, 45.3, 52.0, 53.6, 54.9, 57.0, 57.2, 116.1 (q, J=292.6 Hz, CF_3), 161.4 (q, J=36.3 Hz, $COCF_3$), 165.2 (NHCO), 168.0 (CO_2Me). IR (KBr): 3436, 2958, 1679, 1448, 1208, 1140, 842, 800, 724, 517 cm^{-1}. MS (ES): 313 [M+1]$^+$ (100%). Anal. Calcd for $C_{21}H_{31}F_9N_4O_9$: C, 38.54; H, 4.77; N, 8.56. Found: C, 38.75; H, 5.03; N, 8.91.

3.1.14. Synthesis of (2*S*)-2-{(2*S*)-2-amino[1-(*tert*-butoxycarbonyl)piperidin-(2*R*)-yl]acetyl}amino-2-[1-(*tert*-butoxycarbonyl)piperidin-(2*R*)-yl]acetic acid, 7c. From a solution of **7b** (63 mg, 0.123 mmol) in THF/H_2O and LiOH/H_2O (10 mg, 0.246 mmol) according to the procedure described for **4m** (16 h) was obtained a crude product of **7c** (56 mg, 0.112 mmol, 91%) as a white solid that did not require further purification. Data for **7c**: ^{1}H NMR (300 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 1.41–1.56 (m, 30H, 18H *t*-Bu Boc, 12H pip-H), 2.71 (m, 2H, pip-H-6′$_{ax}$, pip-H-6″$_{ax}$), 3.89 (m, 3H, C*H*NH_2, pip-H-6′$_{eq}$, pip-H-6″$_{eq}$), 4.24 (m, 1H, pip-H-2″), 4.52 (m, 1H, pip-H-2′), 4.77 (m, 1H, H-2), 8.97+9.14 (2 br s, 1H, CO_2H). IR (KBr): 3350, 2920, 2848, 1689, 1450, 1414, 1364, 1273, 1162, 1046 cm^{-1}. MS (ES): 1019 [2M+Na]$^+$, 521 [M+Na]$^+$, 499 [M+1]$^+$ (100%).

3.1.15. Synthesis of (2*R*,2′*R*)-2,2′-[3,6-dioxopiperazino-(2*S*,5*S*)-diyl]dipiperidinium bis(trifluoroacetate), 8b·2TFA. Diketopiperazine **8a** was prepared by two different pathways. (a) A solution of **7b** (30 mg, 0.058 mmol) in DMF (2 mL) was stirred under reflux until disappearance of the starting material monitored by TLC (40 h). The solvent was evaporated under reduced pressure to obtain a crude mixture that was purified by column chromatography (0–2% MeOH/CH_2Cl_2) and crystallization (CH_2Cl_2/hexane) to afford **8a** (6 mg, 0.012 mmol, 22%) as a white solid. (b) To a solution of **7b** (52 mg, 0.102 mmol) in DMF (2 mL) was added 1.8 equiv of KCN (12 mg, 0.182 mmol). The mixture was stirred at 80 °C for 60 h and then was added 2.0 equiv more of KCN (14 mg, 0.204 mmol). After 72 h (monitored by TLC) the reaction was diluted with Et_2O (4 mL) and washed with a saturated solution of NaCl, 0.5 M aqueous solution of H_3PO_4, and a saturated solution of $NaHCO_3$. Finally, the combined aqueous layers were extracted with $CHCl_3$ and the organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product that was purified by column chromatography (0–2% MeOH/CH_2Cl_2) to yield **8a** (14 mg, 0.030 mmol, 29%) as a white solid. Subsequently, from a solution of **8a** (20 mg, 0.042 mmol) in CH_2Cl_2/TFA (0.4 mL) according to the procedure for **7d**, was isolated **8b·2TFA** (15 mg, 0.031 mmol, 75%) after crystallization (Et_2O/CH_2Cl_2) as a white solid. Data for *di(tert-butyl) (2R,2′R)-2,2′-[3,6-dioxo-piperazino-(2S,5S)-diyl] dipiperidine-1-carboxylate,* ***8a***: R_f=0.14 (5% MeOH/CH_2Cl_2). MS (ES): 503 [M+Na]$^+$ (100%). Data for **8b·2TFA**: ^{1}H NMR (CD_3OD, 500 MHz) δ 1.57–1.64 (m, 4H, pip-H), 1.72–1.75 (m, 2H, pip-H), 1.93–1.95 (m, 2H, pip-H), 2.02–2.06 (m, 4H, pip-H), 3.02 (ap t, 2H, J=12.2 Hz, pip-H-6′$_{ax}$, pip-H-6″$_{ax}$), 3.42 (ap d, 2H, J=9.8 Hz, pip-H-2′, pip-H-2″), 3.49 (ap d, 2H, J=12.7 Hz, pip-H-6′$_{eq}$, pip-H-6″$_{eq}$), 4.50 (ap s, 2H, H-2, H-5). ^{13}C NMR (CD_3OD, 100 MHz) δ 23.1 (2C), 23.4 (2C), 24.1 (2C), 47.1 (2C), 55.5 (2C), 58.6 (2C), 168.0 (2C, CO). IR (KBr): 3436, 2946, 2851, 1674, 1631, 1449, 1205, 1051, 773 cm^{-1}. MS (ES): 281 [M−2TFA+1]$^+$ (100%).

3.1.16. (2*S*)-2-({[(2*S*)-2-Amino-2-piperidin-(2*R*)-yl]-acetyl}amino)-2-[piperidin-(2*R*)-yl]acetic acid, 7e. To a solution of **7d** (24 mg, 0.037 mmol) in Et_2O (40 mL/mmol) was added a solution of 10% aqueous NaOH (40 mL/mmol). The mixture was stirred at room temperature for 26 h and the layers were separated. The aqueous phase was lyophilized and the solid residue was triturated with a 10% solution of MeOH/CH_2Cl_2 (5×2 mL). Finally, the organic extracts were concentrated under reduced pressure to afford **7e** (11 mg, 0.037 mmol) as a white solid without further purification. Data for **7e**: ^{1}H NMR (CD_3OD, 300 MHz) δ 1.28–1.60 (m, 6H, pip-H), 1.60–1.86 (m, 6H, pip-H), 2.67 (ap t, 2H, J=10.5 Hz, pip-H-6′$_{ax}$, pip-H-6″$_{ax}$), 2.77 (m, 1H, pip-H-2″), 3.01 (m, 1H, pip-H-2′), 3.12 (ap d, 2H, J=11.5 Hz, pip-H-6′$_{eq}$, pip-H-6″$_{eq}$), 3.27 (d, 1H, J= 5.9 Hz, C*H*NH_2), 4.29 (d, 1H, J=4.9 Hz, H-2), 8.59 (br s, 1H, OH). ^{13}C NMR (CD_3OD, 75 MHz) δ 23.3, 23.4 (2C), 24.6, 27.4, 27.8, 45.5 (2C), 57.6, 58.2, 58.6, 58.9, 168.4 (CO–NH), 174.9 (CO_2H). IR (KBr): 3397, 2925, 2860, 1729, 1652, 1437, 1024 cm^{-1}. MS (ES): 619 [2M+Na]$^+$, 597 [2M+1]$^+$, 321 [M+Na]$^+$, 299 [M+1]$^+$ (100%).

3.1.17. Synthesis of 2,2′-[3,6-dioxopiperazine-(2*S*,5*S*)-diyl]dipiperidinium bis(trifluoroacetate), 8b·2TFA. To a solution of **7d·3TFA** (24 mg, 0.036 mmol) in MeOH/H_2O 1:1 (7.2 mL) was added a solution of 0.1 M aqueous NaOH (0.56 mL) until pH=8.0. The reaction mixture was stirred at room temperature for 16 days and then the organic solvent was evaporated under reduced pressure and the aqueous residue was lyophilized to obtain a solid that was purified

by SCX resin to give **8b** as a mixture of diastereoisomers (10 mg, 0.018 mmol, 99%). Subsequently, from a solution of **8b** (10 mg, 0.036 mmol) in CH_2Cl_2/TFA (0.3 mL) according to the procedure described for **7d** was isolated **8b·2TFA** after crystallization (Et_2O/CH_2Cl_2) as an equimolecular mixture of three diastereoisomers (16 mg, 0.034 mmol, 93%). Data for the mixture of **8b**: $[\alpha]_D^{20}$ +3.9 (*c* 0.69, MeOH). ^{1}H NMR (CD_3OD, 400 MHz) δ 1.33–1.57 (m, 5H, pip-H), 1.59–1.79 (m, 4H, pip-H), 1.85–1.97 (m, 3H, pip-H), 2.66 (m, 2H, pip-H-6′$_{ax}$, pip-H-6″$_{ax}$), 2.99 (m, 2H, pip-H-2′, pip-H-2″), 3.13 (ap d, 2H, *J*=10.8 Hz, pip-H-6′$_{eq}$, pip-H-6″$_{eq}$), 3.99 (m, 2H, H-3, H-6). ^{13}C NMR (CD_3OD, 100 MHz) δ 25.2, 25.4, 26.7, 27.2, 28.2, 29.0, 47.7 (2C), 59.4, 59.6, 60.4, 60.7, 168.7 (NH–CO), 169.4 (NH–CO). IR (KBr): 3361, 2925, 2859, 1667, 1441, 1066, 1048 cm^{-1}. MS (ES): 583 [2M+Na]$^+$, 303 [M+Na]$^+$, 299 [M+H_2O+1]+, 281 [M+1]$^+$ (100%), 198 [M−pip]$^+$. Partial data for the mixture of **8b·2TFA**: ^{1}H NMR (CD_3OD, 300 MHz) δ 1.61–1.68 (m, 4H, pip-H), 1.73–1.76 (m, 2H, pip-H), 1.93–1.96 (m, 2H, pip-H), 2.02 (m, 4H, pip-H), 3.06 (m, 2H, *J*=12.2 Hz, pip-H-6′$_{ax}$, pip-H-6″$_{ax}$), 3.49+3.63 (2m, 4H, *J*=9.8 Hz, pip-H-2′, pip-H-2″, pip-H-6′$_{eq}$, pip-H-6″$_{eq}$), 4.28+4.35+4.56+4.50 (4m, 2H, H-2, H-5).

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6. Under conditions reported in Ref. 5a this imidazolidine led to (2*S*,3*R*,S_S)-*N*-[2-(benzylamino)-1-hydroxyheptan-3-yl] *p*-tolylsulfinamide, **2** (R^1=Bu, R^2=CH_2OH): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.58 (t, 3H, *J*=6.8 Hz), 0.66–1.10 (m, 4H), 1.19–1.37 (m, 2H), 2.34 (s, 3H), 2.60 (ddd, 1H, *J*=7.1, 4.7, 2.7 Hz), 3.18 (m, 1H), 3.49 (dd, 1H, *J*=11.7, 7.1 Hz), 3.58 (dd, 1H, *J*=11.7, 4.6 Hz), 3.64 (d, 1H, *J*=13.0 Hz), 3.79 (d, 1H, *J*=13.0 Hz), 4.89 (d, 1H, *J*=8.4 Hz), 7.09–7.37 (m, 7H), 7.50 (d, 2H, *J*=8.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 21.7, 22.4, 28.1, 34.2, 51.9, 53.3, 59.3, 62.0, 126.4 (2C), 127.6, 128.6 (2C), 128.9 (2C), 129.8 (2C), 140.6, 140.7, 141.9. IR (film): 3434, 2924, 2854, 1631, 1455, 1261, 1034, 906, 700 cm^{-1}. EM (ES): 375 [M+1]$^+$ (100%).

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13. Other conditions for cyclization of **7b** led to complex reaction mixtures: xylene/NEt_3/Δ, 2-butanol/NEt_3/100 °C, and $AlMe_3$/CH_2Cl_2/40 °C. At this point we have attributed the lack of reactivity to conformational restrain induced by the *N*-Boc-piperidine side chains.

14. Failed conditions for cyclization of **7d** led to complex reaction mixtures: *i*-PrOH/NMM/HOAc/Δ, DMF/py/80 °C, and toluene/NEt_3/Δ. Epimerizations among other side reactions could be behind the lack of success.

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