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FULL PAPER

Nitroprolinates as nucleophiles in Michael-type additions and acylations. Synthesis of enantiomerically enriched fused aminopyrrolidino-[1,2-*a*]pyrazinones and -diketopiperazines

Eduardo García-Mingüens,[a][b][c] Verónica Selva,[a][b][c] Olatz Larrañaga,[b][d] Carmen Nájera,[a][b] José M. Sansano,*[a][b][c] and Abel de Cózar,*[b][d][e]

Dedicated to Prof. H. Ila on the occasion of her 75th birthday.

[a] Mr. E. García-Mingüens, Dr. V. Selva, Prof. C. Nájera, Prof. J. M. Sansano
Departamento de Química Orgánica. Facultad de Ciencias.
Universidad de Alicante, 03080-Alicante, Spain.
E-mail: jmsansano@ua.es
[b] Centro de Innovación en Química Avanzada (ORFEO-CINQA)
[c] Instituto de Síntesis Orgánica (ISO).
Universidad de Alicante, 03080-Alicante, Spain.
[d] Dr. O. Larrañaga, Dr A. de Cózar
Departamento de Química Orgánica I, Facultad de Química
Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU, and Donostia International Physics Center (DIPC), P. K. 1072, E-20018 San Sebastián, Spain.
E-mail: abel.decozar@ehu.eus
[e] IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain

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Abstract: The enantioselective formation of nitroprolinates followed by diastereoselective Michael-type addition onto a second unit of the nitro alkene is studied. The reaction occurred in a one pot-sequential process controlled by the chiral phosphoramidite·silver benzoate complex. The origin of the high diastereoselectivity is studied by DFT computational analysis where the crucial effect of the benzoic acid is justified. The employment of this strategy to the preparation of pyrazine-2-ones is also surveyed, as well as the preparation of diketopiperazines from enantiomerically enriched *exo*-prolinates using conventional *N*-acylation-amination-cyclization steps.

Introduction

Nitroprolinates constitute a small series of compounds whose importance in many scientific areas has recently been demonstrated.[1] For example, optically active polysubstituted nitroprolinates **1** (Figure 1) are important inhibitors of α4,β1-integrin-mediated hepatic melanoma and in a murine model of colon carcinoma metastasis, as well as potent antiadhesive properties in several cancer cell lines.[2,3] Bicyclic heterocycles **2**, have been found as inhibitors of skin cancer.[4] Spiroxindoles **3** increased the mortality of zebrafish embryos,[5] and molecules **4** were tested as antimycobacterials against *M. tuberculosis* H37Rv strain.[6] A family of enantiomerically enriched spironitroprolinates **5** were obtained by our group from imino lactones and nitroalkenes which are currently tested as anticancer agents.[7] The presence of the nitro group in this skeleton induced special conformations of the five membered ring causing spectacular effects in its biological activity and its chemical reactivity.[8]

Diastereomeric *exo*-**6** and *endo*-**6** 4-nitroprolinates have been used as chiral organocatalysts in aldol reactions.[9] *endo*-**6** Preferentially promoted the polymerization of D-lactide, whereas *exo*-**6** preferentially polymerized L-lactide from a racemic mixture.[10] Michael-type addition of ketones to nitroalkenes[11] and a three component ketone-carboxylic acid-nitroalkene cyclization[12] were successfully organocatalyzed by chiral *exo*-**6b** (X = H), providing good to excellent diastereoselections and high enantiomeric ratios. A series of enantiopure tetrasubstituted nitroprolinate surrogates has been designed as scaffolds for proteasome inhibitors with high medicinal prospects.[13] In addition, the NH-D-EhuPhos ligand **7** has been efficiently employed in the 1,3-dipolar cycloadditions (1,3-DC) to yield nitroprolinates and structurally rigid spirocompounds from chiral γ-lactams.[9, 14, 15] *exo*-**6a** Series were employed as amino component in the multicomponent amino-aldehyde-dienophile (AAD)[8] reaction affording chiral cyclohex-2-enyl amines and in two different multicomponent 1,3-cycloadditions furnishing pyrrolizidines.[8,16]

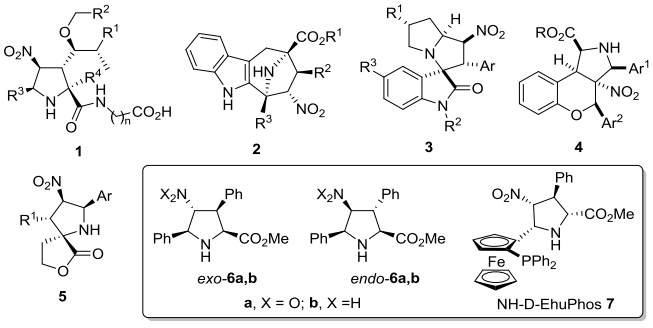
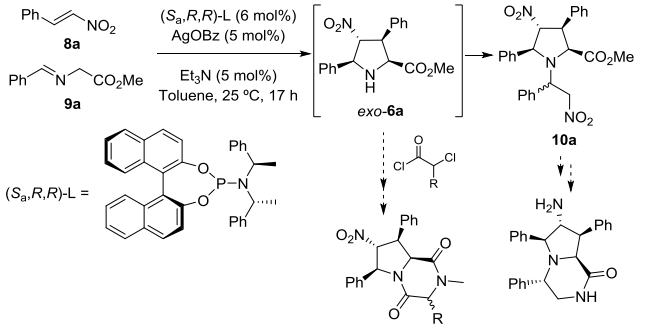


Figure 1. Nitroprolinates with biological properties and utility in organic synthesis.

According to the experience of our group in the synthesis[7] of the enantiomerically enriched nitroprolinates **6**,[17,18] and the reactivity exhibited by the amino moiety of these structures **6**-**7**, we focused our interest in the Michael type addition of the chiral

pyrrolidines **6**. So, in this work we studied the scope and the stereochemical course of the one pot process starting from imino ester **9a** and **8a** to yield compound **10a** (Scheme 1), avoiding the isolation of intermediate *exo*-**6a**. That means, performing a domino enantioselective pyrrolidine formation-diastereoselective Michael addition onto the nitroalkene to provide the corresponding adducts, which can be further transformed into fused nitropyrrolidine-heterocycles. The support of DFT calculations to the mechanistic outcomes, as well as additions of other Michael-type acceptors will be surveyed. In addition, *N*-acylations of **6** with α-chloroacetyl chlorides to provide fused nitropyrrolidine-diketopiperazines will be discussed.

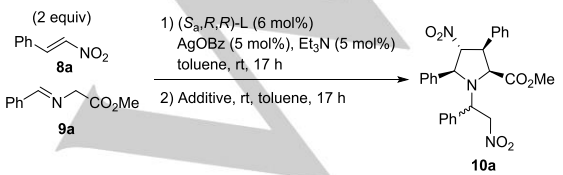


Scheme 1. Design of the synthesis of Michael-type adducts **10** in one pot process from imino ester **9a** for the preparation of fused nitropyrrolidino-pyrazinones and of its acylation for the synthesis of nitropyrrolidino-diketopiperazines.

Results and Discussion

Initially, we employed the conditions for the synthesis of enantiomerically enriched *exo*-**6** compounds, described by our group, but using two equivalents of nitrostyrene. The optimization is briefly summarized in Table 1. Despite the reaction was observed in the presence of the reagents involved in the synthesis of *exo*-cycloadduct **6**, we first tried to perform the reaction of pure *exo*-**6a** with β-nitrostyrene (**8a**) but no reaction product was detected. So, the chiral silver complex has a crucial effect not only in the synthesis of the chiral prolinate but in the Michael-type addition.[19] Basic conditions promoted the retro-Michael type addition obtaining pure *exo*-**6a** cycloadduct (Table 1, entry 1). The addition of several amounts of benzoic acid resulted to be beneficial, the highest amount of acid the highest yield of **10a** was isolated (Table 1, entries 2 and 3). The replacement of benzoic acid by acetic acid was not productive lowering the percentage of **10a** (Table 1, entry 4). The addition of 1.5 or 2.0 equiv of benzoic acid instead of 1 equiv did not improve the results of the reaction.

Table 1. Optimization of the reaction parameters of the synthesis of compound 10a.



entry	additive (equiv)	**6a**:**10a**[a]	yield of **10a** (%)[b]	**10a** dr [c]
1	---	>98:2	---	nd
2	BzOH (0.5)	50:50	nd	>98:2
3	BzOH (1)	<2:98	84%	>98:2
4	AcOH (1)	35:65	nd	>98:2

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield after flash chromatography. Mixture of 4 diastereomers. [c] Determined by ^{1}H NMR of the crude reaction mixture and in the final purified sample.

The absolute configuration of the new stereogenic center was unambiguously determined by both X-ray diffraction analysis and also by vibrational circular dichroism (VCD). In both cases the structure of compound **10a** matched with a (*S*)-configuration[20] (see SI).

In the presence of benzoic acid (1 equiv) at rt during 17 h products **10** were satisfactorily obtained with a very high diastereoselectivity (Figure 2). For compounds **10a**,**c** and **10e** the same nitroalkene was employed for both enantioselective cycloaddition and Michael-type addition. However, it was also possible to introduce a different nitroalkene once the enantioselective cycloaddition took place (Figure 2, products **10b**,**d**). In these examples only one equivalent of nitroalkene was needed in the first step, meanwhile the other different nitroalkene (**8a**, 1 equiv) was added together with the benzoic acid after 17 h. Despite many attempts and combinations of structural parameters in all components of the reaction, the scope was reduced to those examples shown in Figure 2.

The high influence of the chiral silver catalyst in both the 1,3–DC and the Michael addition was analyzed by means of DFT calculations. Within the accepted 1,3–DC reaction mechanism (Scheme 2), the last step consists in the reaction of the silver–pirrolidine **INT3** with fresh imine **9a** to recover the initial azomethine ylide **INT1**[21] and generate final product *exo*–**6a** (Scheme 2, see SI for further details about 1,3–DC analysis). We hypothesize that *exo*–**6a** formation is an irreversible step, and therefore, it is not possible to form **INT3** (and consequently **10a**) by using *exo*–**6a** as starting reagent. In fact, the reaction of isolated *exo*–**6a**, chiral silver(I) complex, β-nitrostyrene **8a**, and benzoic acid did not occur. So, the experimental evidences support that presence of small amounts of **INT3** in this sequential-one pot process is crucial to promote the Michael-type addition.

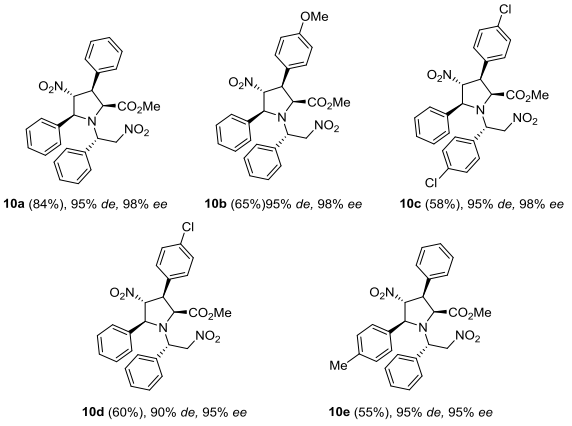


Figure 2. Compounds **10** isolated and characterized.

We postulate that **INT3** can further react with the excess of β-nitrostyrene in the absence of benzoic acid to ultimately form compound **10a** (Scheme 2, route a). Within this route, our calculations shown that formation of **RC2** is only slightly favoured

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(0.3 kcal·mol^{-1}) and the Gibbs' barrier activation is of 9.6 kcal·mol^{-1} (see SI for further details). These results indicate that formation of **10a** by merely adding a second equivalent of β-nitrostyrene to the reaction mixture is not a kinetically favored reaction.

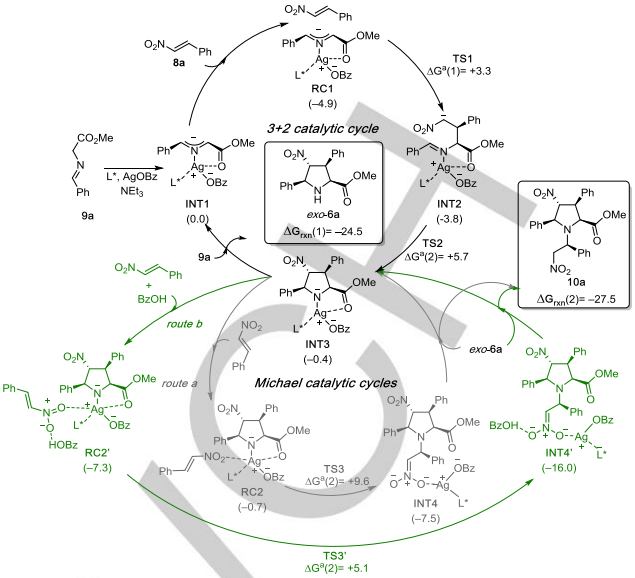
In addition, we also analyzed computationally the effect of adding benzoic acid (Scheme 2, route b). In this case, the additive effect is twofold: firstly, the phenyl ring of benzoic acid interacts with the aromatic rings of the ligand. This π-stacking interaction strongly stabilizes **RC2'** (see SI).[22] Moreover, it enhances β-nitrostyrene electrophilicity (as reflected with the lower activation barrier of **TS3'** compared to **TS3**). Remarkably, both factors prompt **10a** formation.[23]

Exploration of all the possible transition structures associated with the Michael addition step showed the preferential reactivity of the *S*–prochiral face of β-nitrostyrene. The high selectivity can be attributed to the favourable NO_2–Ag interaction (associated with an inward approach of the former) and a stabilizing π-stacking interaction in **TS3'**$_{PRO-S}$ (similar to those found in **RC2'**) that are not present neither in **TS3'**$_{PRO-R}$ (Figure 3) nor in the reaction performed with acetic acid. Note that the relevance of the counteranion in the coordination sphere of the silver atom on the 1,3–DC selectivity was previously assessed.[16a]

Therefore, the calculations predict the preferential formation of compound **10a** with a theoretical *dr* of >99% when using benzoic acid as additive, in excellent agreement with the experimental results.

Another Michael-type addition was successfully tested following the same sequential strategy (Scheme 3). Methyl vinyl ketone afforded product **11** in 78% yield, but acrylates did not work. To overcome this problem a stabilizing group was attached to the electron-withdrawing entity in order to avoid the retro-addition. Thus, compounds **12** and **13** could be isolated in 62% and 71% yields, respectively. An identical situation was observed when 1,1-bis(phenylsulfonyl)ethylene was allowed to react under these optimized conditions furnishing product **14** in 72% yield. Electron-deficient alkynes were also suitable Michael acceptors such as it was demonstrated in the reactions with dimethyl acetylenedicarboxylate and but-3-in-2-one. All these products **11**-**16** were very sensitive to silica-gel purification, so they were isolated from recrystallization from the crude reaction mixtures. Relative configuration of compounds **15** and **16** was determined by nOe experiments (see SI). Again, the reactions between starting nitroprolinate *exo*-**6a** with all these Michael-type acceptors were unsuccessful.

As useful application of the structure **10a** we envisaged the possibility to prepare hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones. For the preparation of bicyclic δ-lactam **18**, compound **10a** was treated with Zn (dust) in the presence of concentrated aqueous HCl (37%) in ethanol at 60 ºC for 15 min[24] (Scheme 4) affording the diamine **17** in 87% yield. The cyclization in methanolic KOH was achieved to generate **18** in 89% yield. In both transformations any epimerization of the five stereocenters was detected.



Scheme 2. Proposed catalytic cycles associated with the 1,3–DC and Michael reaction. Relative and activations Gibbs free energies computed at M06(PCM)/6-311+G**&LANL2DZ// ONIOM(B3LYP/6-31G*&LANL2DZ:UFF) level are in kcal·mol^{-1}.

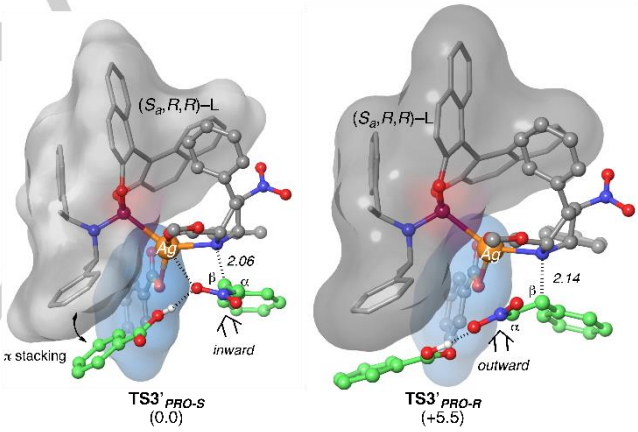


Figure 3. Main geometrical features and relative Gibbs Free energies of transition structures associated with the Michael addition step in presence of benzoic acid as additive computed at M06(PCM)/6-311+G**&LANL2DZ// ONIOM(B3LYP/6-31G*&LANL2DZ:UFF) level. Second molecule of β-nitrostyrene and the additive are highlighted in green. Relative Gibbs free energies and distances are in kcal·mol^{-1} and Å respectively.

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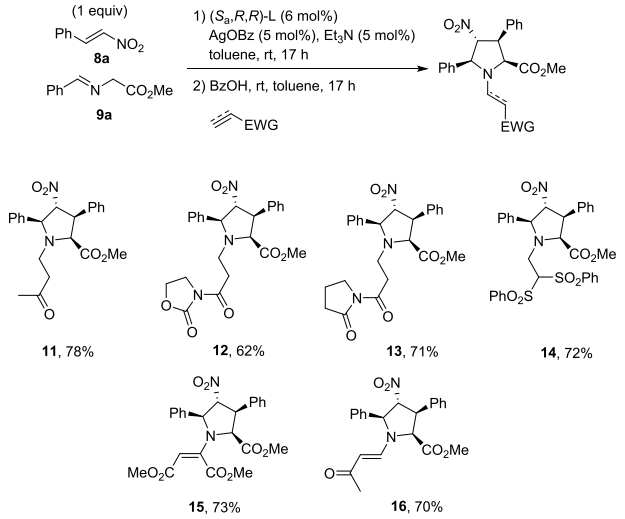
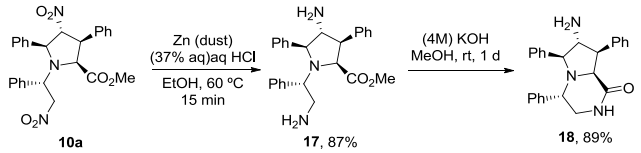
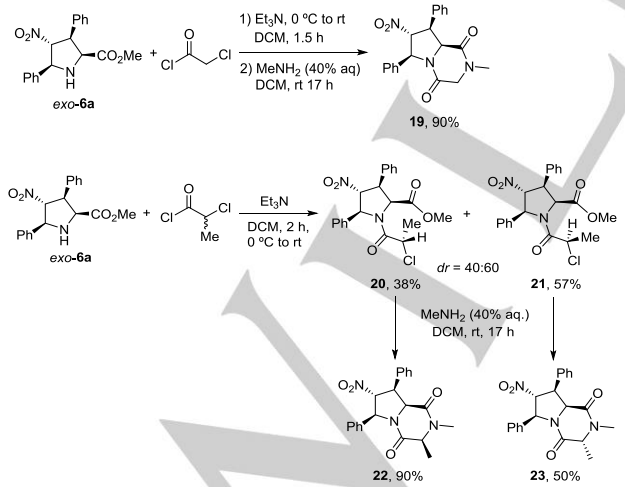


Scheme 3. Sequential enantioselective synthesis of nitroprolinates-Michael type addition.



Scheme 4. Synthesis of enantiomerically enriched pyrazine-2-one **18**.

Besides, 2,5-diketopiperazines, a family of very interesting compounds,[25] were readily prepared from *exo*-**6a** and α-chloro acyl chlorides in very good yields[26] (Scheme 5). The mixture of diastereoisomers **20** and **21** could be separated and independently cyclized employing aqueous methylamine. Their absolute configuration was unambiguously determined according to nOe experiments (see SI).



Scheme 5. Synthesis of diketopiperazines **19**, **22** and **23**.

Conclusion

In conclusion, the enantioselective cycloaddition →diastereoselective Michael-type domino process was satisfactorily controlled. It was demonstrated the crucial effect shown by the chiral phosphoramidite/silver benzoate complex in the almost total diastereoselective control in the Michael-type addition of the intermediate chiral silver prolinamide onto a second unit of β-nitrostyrene. The retro-Michael step can be controlled despite of the lower energetic barrier to yield starting cycloadduct. The presence and position of the benzoic acid is crucial for the activation of the nitroalkene. Its extra π-interaction with the aromatic part of the chiral ligand, together with the repulsive Pauling interaction between the nitro group of β-nitrostyerne and the carboxy moiety of the pyrrolidine ring favour the matching TS arrangement. The scope of this reaction is limited due to the scarce energy gap between the both associated cycles operating simultaneously, which can be more similar depending on the nature of the substituents in both the dipole and the dipolarophile. This methodology allows the diastereoselective synthesis of pyrazin-2-ones in very good yields.

Experimental Section

General: All commercially available reagents and solvents were used without further purification, only aldehydes were also distilled prior to use. Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates, and the spots were visualized under UV light (λ = 254 nm). Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. Optical rotations were measured on a JASCO P-1030 polarimeter with a thermally jacketed 5 cm cell at approximately 25 ˚C and concentrations (*c*) are given in g/100 mL. The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT) are listed and wavenumbers are given in cm^{-1}. NMR spectra were obtained using a Bruker AC-300 or AC-400 and were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR, using $CDCl_3$ as solvent and TMS as internal standard (0.00 ppm) unless otherwise stated. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet or unresolved and br s = broad signal. All coupling constants (*J*) are given in Hertz (Hz) and chemical shifts in ppm. ^{13}C NMR spectra were referenced to $CDCl_3$ at 77.16 ppm. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000 by injection or DIP; fragment ions in *m/z* are given with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were measured on an instrument using a quadrupole time-of-flight mass spectrometer (QTOF) and also through the electron impact mode (EI) at 70 eV using a Finnigan VG Platform or a Finnigan MAT 95S. Vibrational Circular Dichroism (VCD) studies were accomplished in a Jasco FVS-6000 and X-ray crystal structure was determined using a Bruker CCD-Apex.

*General procedure A: Synthesis of Michael adducts (**10**-**16**):* Silver benzoate (5 mol%, 0.026 mmol, 5.9 mg) and (S_a,*R*,*R*)-L (6 mol%, 0.03 mmol, 17.1 mg) were dissolved in toluene (5 mL). After 1 hour stirring the α-imino ester (136 mg, 0.53 mmol) and triethylamine (5 mol%, 0.026 mmol, 3.6 µL) were added. Then,

nitrostyrene (1 equiv, 80 mg) was introduced and the reaction mixture was left to stir for 17 hours. Next, benzoic acid (1 equiv, 64.7 mg) and the corresponding Michael acceptor (1.1 equiv) were added to the solution. The mixture was stirred 17 hours. The crude was filtered through a pad of celite and the filter was washed with EtOAc (15 mL). The corresponding solution was concentrated under reduced pressure and the purification step depended on the compound (see characterization data).

General procedure B: Nitro group reduction (17): A round bottom flask was charged with the Michael adduct **10a** (47.5 mg, 0.1 mmol), zinc powder (261.52 mg, 4 mmol) and ethanol (3 mL). The corresponding suspension was heated to 60 ºC and the hydrochloric acid (37% aq., 0.5 mL) was added drop wise observing formation of hydrogen. The mixture was checked by TLC until completion of the reaction (15 minutes). The solvent was removed under reduced pressure and the grey solid was washed with saturated aqueous potassium carbonate until pH 10 and extracted with dichloromethane (8 mL) three times. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure obtaining a white solid after precipitation/recrystallization (CH_2Cl_2/*n*-Hexane).

*General procedure C: Formation of δ-lactam **18**:* A round bottom flask was charged with **17** (41.5 mg, 0.1 mmol) in a 4 M solution of KOH/MeOH (2 mL). The mixture was stirred at room temperature for 20 hours and the crude mixture was concentrated under reduced pressure, washed with water and extracted with dichloromethane three times. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum obtaining a single diastereoisomer, as a white solid, that was purify by precipitation with CH_2Cl_2/*n*-hexane.

*General procedure D: Formation of diketopiperazine **19** (Method D.1):* To a solution of *exo*-**6a**[17] (0.5 mmol, 163 mg) and triethylamine (1.5 equiv, 0.75 mmol, 105 µL) in dichloromethane (10 mL) at 0 ºC was added chloroacetyl chloride (1.5 equiv, 0.75 mmol, 60 µL). The reaction was stirred for 30 min. at 0 ºC and warmed to room temperature. After being stirred for another 1 hour, the reaction mixture was quenched with water (10 mL) and extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated under reduce pressure. The crude mixture obtained was dissolved in dichloromethane (10 mL) follow by the addition of methylamine (40% aq., 4 mL). The mixture was stirred overnight. The resulting yellow solution was quenched with water (10 mL) and extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated under reduce pressure. The desired product was obtained without purification.

*General procedure D: Formation of diketopiperazines **22** and **23** (Method D.2):* To a solution of *exo*-**6a** (0.18 mmol, 60 mg)[17] and triethylamine (1.5 equiv, 38 µL) in dichloromethane (4 mL) at 0 ºC was added 2-chloropropionylchloride (1.5 equiv, 27 µL) The reaction was stirred for 30 min. at 0 ºC and warmed to room temperature. After being stirred for another 2 hours, the reaction mixture was quenched with water (4 mL) and extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated under reduce pressure. The crude mixture was purified by column chromatography (Hx:EtOAc; 9:1 to 7:3) obtaining both diastereoisomers (dr = 60:40). Each diastereoisomer (50 mg, 0.12 mmol) was dissolved in dichloromethane (3 mL) follow by the addition of methylamine (40% aq., 1.5 mL). The mixture was stirred overnight. The resulting yellow solution was quenched with water (3 mL) and extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated under reduce pressure. The desired products were obtained by purification by column chromatography (Hx:EtOAc; 7:3).

(2*S*,3*S*,4*R*,5*S*)-Methyl 4-nitro-1-[(*S*)-2-nitro-1-phenylethyl]-3,5-diphenylpyrrolidine-2-carboxylate (10a). White solid (211 mg, 84% yield, *de*: 95%); precipitation with EtOAc:Et_2O; mp: 154-158 °C; $[\alpha]_D^{26}$ = 51.2 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.41 (s, 3H, CO_2CH_3), 3.84 (dd, *J* = 11.5, 9.8 Hz, 1H, NCHC*H*Ph), 4.29 (d, *J* = 9.8 Hz, 1H, C*H*CO_2Me), 4.62-4.44 (m, 3H, CH_2, NC*H*$CHNO_2$), 4.85 (dd, *J* = 12.1, 9.1 Hz, 1H, NC*H*CH_2NO_2), 5.54 (dd, *J* = 11.5, 8.8 Hz, 1H,C*H*NO_2), 7.08-7.14 (m, 2H, Ar*H*), 7.22-7.28 (m, 5H, Ar*H*), 7.44-7.60 (m, 8H, Ar*H*) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 51.2 (NCH*C*HPh), 52.2 (O*C*H_3), 60.6 (N*C*HPh), 63.4 (N*C*HPh), 70.3 (*C*CO_2Me), 77.4 (*C*H_2NO_2), 91.8 (*C*HNO_2), 127.9, 128.0, 128.3, 128.9, 129.5, 129.6, 129.7, 129.9, 132.4, 136.7 (Ar*C*), 172.1 (*C*O_2Me) ppm; IR (ATR) υ_{max}: 1743, 1552, 1376, 1195, 1140 cm^{-1}; MS (EI): *m/z* 429 (M^+-NO_2, <2%), 417 (16), 416 (63), 370 (21), 369 (80), 279 (12), 221 (18), 220 (100), 219 (36), 194 (14), 193 (80), 191 (13), 178 (19), 117 (22), 116 (16), 115 (58), 105 (13), 104 (79), 103 (17), 102 (11), 91 (27), 77 (20); HRMS calcd. for $C_{26}H_{25}N_3O_6$(–$CH_4N_2O_4$) 367.1561; found: 367.1576.

(2*S*,3*S*,4*R*,5*S*)-Methyl 3-(4-methoxyphenyl)-4-nitro-1-[(*S*)-2-nitro-1-phenylethyl]-5-phenylpyrrolidine-2-carboxylate (10b). White solid (174 mg, 65% yield, *de*: 95%); precipitation with EtOAc:Et_2O; mp: 162-167 °C; $[\alpha]_D^{28}$ = 83.2 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.45 (s, 3H, CO_2CH_3), 3.74 (s, 3H, $COCH_3$), 4.24 (d, *J* = 9.8 Hz, 1H, C*H*CO_2Me), 4.44-4.59 (m, 3H, CH_2, NC*H*$CHNO_2$), 4.80 (dd, *J* = 12.2, 9.3 Hz, 1H, NC*H*CH_2NO_2), 5.49 (dd, *J* = 11.6, 8.8 Hz, 1H,C*H*NO_2), 6.77-7.02 (m, 2H, Ar*H*), 7.02-7.22 (m, 2H, Ar*H*), 7.22-7.24 (m, 2 H, Ar*H*), 7.46-7.56 (m, 8H, Ar*H*) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 50.81 (NCH*C*HPh), 52.2 (O*C*H_3), 55.4 (PhO*C*H_3), 60.6 (N*C*HPh), 63.5 (N*C*HPh), 70.2 (*C*CO_2Me), 77.2 (*C*H_2NO_2), 92.2 (*C*HNO_2), 114.4, 124.2, 128.0, 128.4, 129.2, 129.6, 129.7, 129.9, 132.6, 136.9, 159.8, (Ar*C*), 172.3 (*C*O_2Me) ppm; IR (ATR) υ_{max}: 1739, 1612, 1552, 1517, 1494, 1455, 1436, 1373, 1305, 1253, 1139, 1091, 1029, 981, 921, 701 cm^{-1}; MS (EI): *m/z* 459 (M^+-NO_2, <2%), 446 (19), 399 (25), 250 (30), 249 (13), 223 (100), 145 (14), 116 (19), 113 (22), 91 (15), 77 (15); HRMS calcd. for: $C_{27}H_{27}N_3O_7$(–NO_2) 459.1920; found: 459.1906.

(2*S*,3*S*,4*R*,5*S*)-Methyl 3-(4-chlorophenyl)-1-[(*S*)-1-(4-chlorophenyl)-2-nitroethyl]-4-nitro-5-phenylpyrrolidine-2-carboxylate (10c). White solid (167 mg, 58% yield, *de*: 95%); precipitation with EtOAc:Et_2O; mp: 184-189 °C; $[\alpha]_D^{28}$ = 68.4 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.44 (s, 3H, CO_2CH_3),), 3.84 (dd, *J* = 11.5, 9.8 Hz, 1H, NCHC*H*Ph), 4.18 (d, *J* = 9.8 Hz, 1H, C*H*CO_2Me), 4.44-4.59 (m, 3H, CH_2, NC*H*$CHNO_2$), 4.80 (dd, *J* = 12.2, 9.3 Hz, 1H, NC*H*CH_2NO_2), 5.49 (dd, *J* = 11.6, 8.8 Hz, 1H,C*H*NO_2), 7.06-7.52 (13 H, Ar*H*) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 50.7 (NCH*C*HPh), 52.5 (O*C*H_3), 60.1 (N*C*HPh), 63.6 (N*C*HPh), 70.3 (*C*CO_2Me), 77.0 (*C*H_2NO_2), 91.9 (*C*HNO_2), 128.0, 128.3, 128.7, 129.3, 129.4, 129.7, 129.7, 130.0, 130.2, 130.4, 130.9, 131.1, 134.9, 136.0, 136.4 (Ar*C*), 171.9 (*C*O_2Me) ppm; IR (ATR) υ_{max}: 1740, 1687, 1553, 1492, 1365, 1324, 1290, 1202, 1091,

1014, 819, 704 cm^{-1}; MS (EI): *m/z* 429 (M$^+$-NO$_2$, <2%), 417 (16), 416 (63), 370 (21), 369 (80), 279 (12), 221 (18), 220 (100), 219 (36), 194 (14), 193 (80), 191 (13), 178 (19), 117 (22), 116 (16), 115 (58), 105 (13), 104 (79), 103 (17), 102 (11), 91 (27), 77 (20); HRMS calcd. for: $C_{26}H_{23}Cl_2N_3O_6$ 543.0964; found: 543.1017.

(2*S*,3*S*,4*R*,5*S*)-Methyl 3-(4-chlorophenyl)-4-nitro-1-[(*S*)-2-nitro-1-phenylethyl]-5-phenylpyrrolidine-2-carboxylate (10d). White solid (193 mg, 60% yield, *de:* 90%); precipitation with EtOAc:Et$_2$O; mp: 170-172 °C; $[\alpha]_D^{28}$ = 74.7 (*c* 1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 3.46 (s, 3H, CO$_2$C*H*$_3$), 3.78 (dd, *J* = 11.3, 10.0 Hz, 1H, NCHC*H*Ph) 4.27 (d, *J* = 9.8 Hz, 1H, C*H*CO$_2$Me), 4.38-4.60 (m, 3H, C*H*$_2$, NC*H*CHNO$_2$), 4.85 (dd, *J* = 12.2, 9.4 Hz, 1H, NC*H*CH$_2$NO$_2$), 5.49 (dd, *J* = 11.5, 8.8 Hz, 1H,C*H*NO$_2$), 7.04-7.56 (m, 14H, Ar*H*) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 50.6 (NCH*C*HPh), 52.4 (O*C*H$_3$), 60.6 (N*C*HPh), 63.3 (N*C*HPh), 70.3 (*C*CO$_2$Me), 77.18 (*C*H$_2$NO$_2$), 91.8 (*C*HNO$_2$), 128.1, 128.3, 128.4, 129.2, 129.3, 129.4, 129.5, 129.6, 129.7, 129.9, 130.0, 131.0, 132.4, 134.7, 136.6 (Ar*C*), 172.0 (*C*O$_2$Me) ppm; IR (ATR) υ_{max}: 1731, 1547, 1494, 1376, 1204, 1146, 1093, 1031, 1015, 839, 808, 767 cm^{-1}; MS (EI): *m/z* 449 (M$^+$-CH$_2$NO$_2$, <2%), 439 (18), 437 (25), 151 (11), 149 (23), 139 (23), 137 (71), 135 (15), 117 (17), 116 (12), 115 (35), 102 (20), 101 (18), 256 (25), 253 (72), 229 (32.5), 227 (100), 219 (15), 192 (24), 191 (21), 189 (13)151 (11), 149 (23), 136 (15), 125 (17), 116 (26), 115 (35), 102 (20), 91 (13), 77 (10); HRMS calcd. for: $C_{26}H_{25}N_3O_6$(–CO_2CH_3) 450.1221; found: 450.1252.

(2*S*,3*S*,4*R*,5*S*)-Methyl 4-nitro-1-[(*S*)-2-nitro-1-phenylethyl]-3-phenyl-5-(*p*-tolyl)pyrrolidine-2-carboxylate (10e): White solid (144 mg, 55% yield, *de*: 95%); precipitation with EtOAc:Et$_2$O; mp: 171-172 °C; $[\alpha]_D^{26}$ = 50.8 (*c* 1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 2.42 (s, 3H, PhCH$_3$), 3.39 (s, 3H, CO$_2$C*H*$_3$), 3.78-3.88 (m, 1H, NCHC*H*Ph) 4.27 (d, *J* = 9.9 Hz, 1H, C*H*CO$_2$Me), 4.44-4.53 (m, 2H, C*H*$_2$), 4.59 (dd, *J* = 9.1, 6.2 Hz, NC*H*CHNO$_2$) , 4.84 (dd, *J* = 12.2, 9.2 Hz, 1H, NC*H*CH$_2$NO$_2$), 5.51 (dd, *J* = 11.5, 8.8 Hz, 1H,C*H*NO$_2$), 7.09-7.52 (m, 14H, Ar*H*) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 21.6 (PhCH3), 51.2 (NCH*C*HPh), 52.2 (O*C*H$_3$), 60.5 (N*C*HPh), 63.5 (N*C*HPh), 70.2 (*C*CO$_2$Me), 77.2 (*C*H$_2$NO$_2$), 91.9 (*C*HNO$_2$), 128.0, 128.4, 128.6, 129.0, 129.7, 129.7, 130.3, 130.4, 132.6, 132.6, 134.0, 139.8 (Ar*C*), 172.3 (*C*O$_2$Me) ppm; IR (ATR) υ_{max}: 1741, 1552, 1453, 1434, 1369, 1199, 1141, 1025, 816 cm^{-1}; MS (EI): *m/z* 443 (M$^+$-NO$_2$, 2%), 431 (20), 430 (72), 384 (28), 383 (100), 235 (15), 234 (82), 233 (44), 207 (43), 191 (13), 131 (12), 130 (11), 129 (14), 115 (34), 104 (66), 103 (15), 91 (18); HRMS calcd. for: $C_{26}H_{25}N_3O_6$(–CO_2CH_3) 430.1767; found: 430.1769.

(2*S*,3*S*,4*R*,5*S*)-Methyl 4-nitro-1-(3-oxobutyl)-3,5-diphenylpyrrolidine-2-carboxylate (11): White solid (172 mg, 78% yield); mp: 132 ºC; precipitation with EtOAc:Et$_2$O; mp: 142-144 ^{0}C; $[\alpha]_D^{17}$ = 72.0 (*c* 1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.99 (s, 3H, COCH$_3$), 2.61-2.41 (m, 2H,), 3.00 (t, J = 7 Hz, 1H,), 3.29 (s, 3H, CO$_2$CH3), 4.17 (d, J = 9.9 Hz, 1H,), 4.46-4.40 (m, 2H,), 5.39 (dd, J = 9.9, 8.7 Hz,), 7.27-7.56 (m, 10H, ArH) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 30.1 (CO*C*H$_3$), 41.6 (CH$_2$), 47.4 (CH$_2$), 51.2 (NCH*C*HPh), 51.9 (CO$_2$CH$_3$), 69.5 (N*C*HPh), 72.8 (N*C*HCO$_2$CH$_3$), 93.8 (CHNO2), 128.0, 128.1, 128.5, 128.9, 129.2, 129.5, 130.3, 133.7, 134.1, 137.2 (ArC), 171.6 (*C*O$_2$CH$_3$), 206.9 (*C*OCH$_3$) ppm; IR (ATR) υ_{max}: 1742, 1714, 1366, 1147 cm^{-1}; MS (EI): *m/z* 350 (M$^+$-NO2, 32%), 337 (27), 291 (26), 290 (99), 233 (20), 232 (100), 115 (35); HRMS calcd. for: $C_{22}H_{24}N_2O_5$ 396.1685; found: 396.1678.

(2*S*,3*S*,4*R*,5*S*)-Methyl 4-nitro-1-[3-oxo-3-(2-oxooxazolidin-3-yl)propyl]-3,5-diphenylpyrrolidine-2-carboxylate (12): White solid (153 mg, 62% yield); mp: 150-152 ^{0}C; precipitation with EtOAc:Et$_2$O; $[\alpha]_D^{17}$ = 15.6 (*c* 1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 2.98-3.02 (m, 2H), 3.05-3.16 (m, 2H), 3.30 (s, 3H, CO$_2$CH$_3$), 3.87-3.93 (m, 2H), 4.24 (d, J = 9.9 Hz, 1H), 4.30-4.34 (m, 2H), 4.39-4.49 (m, 2H), 5.38 (dd, J = 9.9, 8.7 Hz, 1H), 7.25-7.31 (m, 5H, ArH), 7.39-7.41 (m, 3H), 7.55-7.57 (m, 2H) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 33.2 (NCH$_2$CH$_2$), 42.5 (OCNCH$_2$), 47.5 (NCH2CH2), 51.2 (NCH*C*HPh), 51.8 (CO$_2$CH$_3$), 62.2 (CO$_2$CH$_2$), 69.1 (NCHPh), 72.4 (N*C*HCO$_2$CH$_3$), 93.4 (CHNO$_2$), 128.1, 128.2, 128.4, 128.6, 128.8, 129.1, 129.3, 129.4, 130.2, 134.2, 137.3 (ArC), 153.5 (NCOO), 171.3 (CO), 171.6 (CO) ppm; IR (ATR) υ_{max}: 1794, 1743, 1697, 1541, 1383, 1196 cm^{-1}; MS (EI): 421 (M$^+$ -NO$_2$, 26%), 420 (47), 408 (23), 361 (59), 274 (100), 232 (55), 220 (29), 193 (32), 142 (30), 115 (44), 91 (22), 55 (25); HRMS calcd. for $C_{24}H_{25}N_3O_7$: 467.1693; found: 467.1672.

(2*S*,3*S*,4*R*,5*S*)-Methyl 4-nitro-1-[3-oxo-3-(2-oxopyrrolidin-1-yl)propyl]-3,5-diphenylpyrrolidine-2-carboxylate (13): white solid (172 mg, 71% yield); precipitation with EtOAc:Et$_2$O; mp: 134-136 ^{0}C; $[\alpha]_D^{17}$ = 18.4 (*c* 1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.95-1.98 (m, 2H), 2.47-2.52 (m, 2H), 2.90-2.97 (m, 1H), 3.00-3.13 (m, 3H), 3.30 (s, 3H), 3.70 (td, J = 7.4, 1.6 Hz, 2H), 4.25 (d, J = 10.0 Hz, 1H), 4.38-4.46 (m, 2H), 5.37 (dd, J = 10.0, 8.5 Hz, 1H), 7.25-7.30 (m, 5H), 7.36-7.41 (m, 3H), 7.53-7.56 (m, 2H) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 17.2 (OCNCH$_2$*C*H$_2$), 33.6 (OCNCO*C*H$_2$), 34.8 (NCH$_2$CH$_2$CO), 45.5 (OCN*C*H$_2$CH$_2$), 47.3 (N*C*H$_2$CH$_2$CO), 51.2 (NCH*C*HPh), 51.7 (CO$_2$*C*H$_3$), 68.9 (NCHPh), 72.2 (N*C*HCO$_2$CH$_3$), 94.0 (CHNO$_2$), 128.0, 128.2, 128.3, 128.6, 128.8, 129.1, 129.2, 130.2, 134.3, 137.6 (ArC), 171.7 (CO), 172.2 (CO), 175.4 (CO) ppm; IR (ATR) υ_{max}: 1742, 1685, 1545, 1353 cm^{-1}; MS (EI): 419 (M$^+$ -NO2, 31%), 275 (20), 274 (100), 232 (25), 220 (25), 193 (19), 140 (23), 115 (25); HRMS calcd. for $C_{25}H_{27}N_3O_6$: 465.1900; found: 465.1894.

(2*S*,3*S*,4*R*,5*S*)-Methyl 1-[3,3-bis(phenylsulfonyl)propyl]-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (14): white solid (242.2, 72% yield); precipitation with EtOAc:Et$_2$O; mp: 164-166 ^{0}C; $[\alpha]_D^{17}$ = 22.8 (*c* 1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 3.30 (s, 3H, CO$_2$CH$_3$), 3.61 (dd, J = 16.0, 4.6 Hz, 1H, NCH$_2$), 3.76 (dd, J = 16.5, 3.2 Hz, 1H, NCH$_2$), 4.40-4.46 (m, 2H, NCHC*H*Ph, NCHCO$_2$Me), 4.51 (d, J = 8.1 Hz, 1H, NCHPh), 4.84 (t, J = 4.1 Hz, 1H, CH(SO$_2$Ph)$_2$), 5.35 (dd, J = 12.4, 4.4 Hz, 1H, CHNO$_2$), 7.24-7.72 (m, 20H, ArH) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 48.3 (NCH$_2$), 51.5 (NCH*C*HPh), 51.9 (CH$_3$), 69.7 (NCHPh), 72.4 (N*C*HCO$_2$CH$_3$), 80.9 (CS), 94.5 (CHNO$_2$), 128.2, 128.3, 128.5, 128.9, 129.1, 129.2, 129.4, 129.8, 130.3, 133.7, 134.3, 134.6, 134.7, 137.1, 137.3, 138.0 (ArC), 171.9 (CO) ppm; IR (ATR) υ_{max}: 1739, 1694, 1313, 1143, 1078, 736 cm^{-1}; MS(EI): 437 (20), 423 (14), 422 (77), 421 (60), 363 (26), 362 (100), 330 (31), 303 (11), 302 (40), 298 (15), 277 (31), 271 (17), 270 (68), 244 (21), 243 (25), 193 (41), 178 (26), 115 (94), 91 (42), 77 (29); HRMS calcd. for $C_{18}H_{16}NO_2$: 278.1165; found: 278.1181.

Dimethyl 2-[(2*S*,3*S*,4*R*,5*S*)-2-(methoxycarbonyl)-4-nitro-3,5-diphenylpyrrolidin-1-yl]but-2-enedioate (15): White solid (185.8 mg, 73% yield); mp: 110-112 ^{0}C; $[\alpha]_D^{25}$ = 34.6 (*c* 1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 3.40 (s, 3H, CO$_2$CH$_3$), 3.47 (s, 3H, CO$_2$CH$_3$), 3.56 (s, 3H, CO$_2$CH$_3$), 4.50-4.55 (m, 2H, NCHC*H*Ph,

CCHCO$_2$Me), 4.64 (d, J = 9.2 Hz, 1H, NCHCO$_2$Me), 5.31 (d, J = 8.7 Hz, 1H, NCHPh), 5.71 (dd, J = 11.9, 8.7 Hz, 1H, CHNO$_2$), 7.23-7.25 (m, 2H, ArH), 7.34-7.36 (m, 3H, ArH), 7.39-7.45 (m, 3H, ArH), 7.58-7.59 (m, 2H, ArH) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 50.6 (NCH*C*HPh), 51.3 (CH$_3$), 52.6 (CH$_3$), 52.9 (CH$_3$), 66.9 (NCHPh), 68.3 (N*C*HCO$_2$CH$_3$), 92.0 (C=C), 92.4 (CHNO$_2$), 127.5, 127.9, 129.2, 129.3, 129.4, 129.6, 130.3, 136.1, 149.6, 164.7 (CO$_2$CH$_3$), 166.8 (CO$_2$CH$_3$), 170.2 (CO$_2$CH$_3$) ppm; IR (ATR) υ_{max}: 1694, 1668, 1314, 1124 cm^{-1}; MS (EI): 279 (14), 220 (68), 194 (17), 193 (100), 178 (13), 125 (19), 19 (62), 117 (28), 115 (45), 103 (47), 91 (31), 77 (86); HRMS calcd. for $C_{18}H_{17}NO_2$: 279.1269; found: 279.1232.

(2*S*,3*S*,4*R*,5*S*)-Methyl 4-nitro-1-[(*E*)-3-oxobut-1-en-1-yl]-3,5-diphenylpyrrolidine-2-carboxylate (16): Orange foam (145 mg, 70% yield); $[\alpha]_D^{25}$ = 54.0 (*c* 1, CHCl$_3$) ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.99 (s, 3H, CHCOC*H*$_3$), 3.39 (s, 3H, CO$_2$CH$_3$), 4.51-4.65 (m, 2H, NCHCO$_2$, NCHC*H*Ph), 5.02 (d, *J* = 13.4 Hz, 1H NC*H*CHCO), 5.20 (d, *J* = 8.9 Hz, 1H, NCHPh), 5.70 (dd, *J* = 8.9, 11.4 Hz, 1H, CHNO$_2$), 7.19 (d, *J* = 13.4 Hz, 1H, NCHC*H*CO), 7.25-7.58, (m, 10H, ArH) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 28.0 (CO*C*H$_3$), 50.8 (CO$_2$*C*H$_3$), 52.6 (NCH*C*HPh), 69.9 (*C*HCO$_2$CH$_3$), 76.8 (NCHPh), 91.6 (CHNO$_2$), 102.7 (C=C), 127.2, 127.8, 128.0, 129.2, 129.8, 130.1, 130.7, 135.7, 145.5 (ArC, C=C) 170.1 (*C*O$_2$CH$_3$), 195.7 (*C*OCH$_3$) ppm; MS (EI): *m/z* 349 (25), 348 (100), 306 (12), 288 (33), 244 (16), 193 (11), 115 (29), 91 (13); HRMS calcd. for: $C_{22}H_{22}N_2O_5$ 394.1529; found: 394.1547.

(2*S*,3*R*,4*R*,5*S*)-Methyl 4-amino-1-[(*S*)-2-amino-1-phenylethyl]-3,5-diphenylpyrrolidine-2-carboxylate (17): white foam (87% yield); precipitation with EtOAc:Et$_2$O; mp.: 50-53 °C; $[\alpha]_D^{23}$ = 55.6 (*c* 1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.66 (s, 4H, 2x N*H*$_2$), 2.73 (dd, *J* = 13.5, 5.1 Hz, 1H, NCHC*H*$_2$NH$_2$), 2.85-2.98 (m, 2H, NCHC*H*$_2$NH$_2$, NCHC*H*NH$_2$), 3.21 (s, 3H, CO$_2$C*H*$_3$), 3.59 (dd, *J* = 9.7, 5.1 Hz, 1H, NC*H*CH$_2$NH$_2$), 3.67 (d, *J* = 8.4 Hz, 1H, NC*H*CO$_2$Me), 3.78 (dd, *J* = 11.2, 8.4 Hz, 1H, NCHC*H*Ph), 4.12 (d, *J* = 10.3 Hz, 1H, NC*H*CHNH$_2$), 7.10-7.51 (m, 13H, Ar*H*), 7.74-7.82 (m, 2H, Ar*H*) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 43.9 (NCH*C*H$_2$NH$_2$), 51.6 (NCH*C*HPh), 55.1 (O*C*H$_3$), 60.9 (N*C*HPh), 63.3 (N*C*HPh), 64.9 (NCH*C*HNH$_2$), 73.4 (*C*CO$_2$Me), 127.6, 128.0, 128.3, 128.4, 128.5, 128.6, 128.7, 128.7, 129.1, 136.1, 136.8, 141.5 (Ar*C*), 174.6 (*C*O$_2$Me) ppm; IR (ATR) υ_{max}: 3296, 3216, 1739, 1455, 1265, 1207, 1181, 1144, 1121 cm^{-1}; MS (EI): *m/z* 415 (M$^+$, <1%), 411 (20), 386 (28), 285 (100), 208 (27), 206 (12), 118 (11), 117 (12), 116 (11), 91 (16); HRMS calcd. for: $C_{26}H_{29}N_3O_2$(–CH_2NH_2) 385.1922; found: 385.1916.

(4*S*,6*S*,7*R*,8*R*,8a*S*)-7-Amino-4,6,8-triphenylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (18): yellow solid (33 mg, 89% yield); precipitation with EtOAc:Et$_2$O; mp: 211-215 °C; $[\alpha]_D^{26}$ = 102.5 (*c* 0.7, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.60 (s, 2H, N*H*$_2$), 2.90 (d, *J* = 7.2 Hz, 1H, NC*H*CO), 3.08 (dd, *J* = 8.2, 3.8 Hz, 1H, NCHC*H*NH$_2$), 3.17 (dd, *J* = 7.2, 3.8 Hz, 1H, NCHC*H*Ph), 3.51 (dd, *J* = 11.6, 4.0 Hz, 1H, NCHC*H*$_2$), 3.55 (d, *J* = 8.2 Hz, 1H, NC*H*CHNH$_2$), 4.02 (dd, *J* = 11.6, 5.7 Hz, 1H, NCHC*H*$_2$), 4.08 (d, *J* = 5.7 Hz, 1H, NC*H*CH$_2$), 6.40 (d, *J* = 4.0 Hz, 1H, OCN*H*), 7.08-7.25 (m, 3H, Ar*H*), 7.28-7.41 (m, 6H, Ar*H*), 7.43-7.57 (m, 6H, Ar*H*) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 46.9 (OCNHCH$_2$), 53.5, 62.2 (3x *C*HPh), 69.9 (NCH*C*HNH$_2$), 73.4 (*C*CO), 126.4, 127.3, 128.0, 128.2, 128.2, 128.5, 128.5, 128.9, 129.3, 133.7, 139.4, 144.1 (Ar*C*), 169.9 (O*C*NH) ppm; IR (ATR) υ_{max}: 1670, 1491, 1453, 1348, 1313, 1183, 1110, 1071, 1029, 907, 749, 730 cm^{-1} ;MS (EI): *m/z* 383 (M$^+$, 8%), 265 (34), 264 (100), 248 (13), 247 (64), 208 (11), 206 (13), 161 (52), 160 (28), 130 (16), 119 (23), 118 (17), 117 (15), 104 (20), 103 (13), 91 (19), 90 (11); HRMS calcd. for: $C_{25}H_{25}N_3O$ 383.1998; found: 383.1996.

(6*S*,7*R*,8*S*,8a*S*)-2-Methyl-7-nitro-6,8-diphenylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (19): Yellow solid (163.7 mg, 90% yield); Without purification; mp: 188 ºC; $[\alpha]_D^{25}$ = 417 (*c* 0.6, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 3.03 (s, 3H, NCH$_3$), 3.97 (d, *J* = 17.2, Hz, 1H, CH$_2$), 4.33 (d, *J* = 17.2 Hz, 1H, CH$_2$), 4.42 (dd, *J* = 9.6, 6.9 Hz, 1H, NCHC*H*Ph), 4.72 (d, *J* = 9.6 Hz, 1H, NCHCO), 5.20 (dd, *J* = 6.9, 4.3 Hz, 1H, CHNO$_2$), 5.92 (d, *J* = 4.3 Hz, 1H, NCHPh), 7.09-7.46 (10H, ArH) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 33.9 (NCH$_3$), 53.1 (NCH*C*HPh), 54.2 (NCHPh), 64.2 (CH$_2$), 64.9 (*C*HCO), 96.8 (CHNO$_2$), 125.5, 127.9, 128.4, 129.0, 129.3, 129.7, 136.7, 136.8 (ArC), 161.8 (CO), 164.6 (CO) ppm; IR (ATR) υ_{max}: 2925, 1666, 1554, 1451, 1329, 90 cm^{-1} ;MS (EI): *m/z* 320 (25), 319 (100), 318 (25), 220 (33), 193 (28), 115 (41), 91 (12); HRMS calcd. for: $C_{20}H_{19}N_3O_4$ 365.1376; found: 365.1395

(2*S*,3*S*,4*R*,5*S*)-Methyl 1-[(*R*)-2-chloropropanoyl]-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (21): White foam (126 mg, 38% yield); $[\alpha]_D^{26}$ = 65.9 (*c* 1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.35 (d, *J* = 6.6 Hz, 3H, CCH$_3$), 3.36 (s, 3H, OCH$_3$), 3.76 (q, *J* = 6.6 Hz, 1H, CHCl), 4.44 (dd, *J* = 11.9, 9.5 Hz, 1H, NCHC*H*Ph), 5.10 (d, *J* = 9.5 Hz, 1H, NC*H*CO$_2$CH$_3$), 5.62 (d, *J* = 8.7 Hz, 1H, NCHPh), 5.71 (dd, *J* = 11.9, 8.7 Hz, 1H, CHNO$_2$), 7.25-7.79 (10H, ArH) ppm; ^{13}C NMR (CDCl$_3$) δ_C: 19.8, 49.4, 50.3, 52.3, 65.0, 66.3, 93.3, 127.1, 127.8, 129.2, 130.0, 130.1, 130.8, 137.4, 169.1, 171.0 ppm; IR (ATR) υ_{max}: 1745, 1662, 1560, 1364, 1210, 701 cm^{-1} ;MS (EI): *m/z* 370 (M$^+$-NO$_2$, 27%), 312 (12), 310 (37), 281 (12), 280 (62), 278 (18), 221 (18), 220 (100), 219 (15), 191 (10), 117 (10), 116 (10), 115 (42), 90 (19); HRMS calcd. for: $C_{21}H_{21}N_2O_3$ 370.121; found: 370.1201.

(2*S*,3*S*,4*R*,5*S*)-Methyl 1-[(*S*)-2-chloropropanoyl]-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (20): White foam (190 mg, 57% yield); $[\alpha]_D^{26}$ = 6.2 (*c* 1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: (1:1 mixture of rotamers) 1.57 (d, *J* = 6.6 Hz, 3H, CCH$_3$), 3.37 (s, 1.5 H, OCH$_3$), 3.43 (s, 1.5 H, OCH$_3$), 4.12 (bs, 0.5 H), 4.25 (bs, 0.5H), 4.39 (bs, 0.5 H), 4.54 (bs, 0.5 H), 5.09 (d, 0.5H), 5.32 (d, 0.5H), 5.38 (d, 0.5H), 5.51 (d, 0.5H), 5.51 (d, 0.5H), 5.74 (m, 1H, CHNO$_2$), 7.23-7.74 (10H, ArH) ppm; ^{13}C NMR (CDCl$_3$) δ_C: (Mixture of rotamers) 20.8, 22.0, 49.6, 50.8, 51.0, 51.5, 52.4, 52.8, 64.3, 64.7, 66.7, 67.3, 91.5, 93.4, 126.5, 127.1, 127.8, 128.9, 129.1, 129.3, 130.0, 136.5, 137.6, 167.5, 170.3 ppm; IR (ATR) υ_{max}: 1742, 1669, 1556, 1368, 1214, 700 cm^{-1} ;MS (EI): *m/z* 370 (M$^+$-NO$_2$, 27%), 312 (12), 310 (37), 281 (12), 280 (62), 278 (18), 221 (18), 220 (100), 219 (15), 191 (10), 117 (10), 116 (10), 115 (42), 90 (19); HRMS calcd. for: $C_{21}H_{21}N_2O_3$ 370.121; found: 370.1201.

(3*S*,6*S*,7*R*,8*S*,8a*S*)-2,3-Dimethyl-7-nitro-6,8-diphenylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (23): Colorless oil (40 mg, 90% yield); $[\alpha]_D^{25}$ = 14.4 (*c* 1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 1.69 (d, J = 6.9 Hz, 3H, CHC*H*$_3$), 3.03 (s, 3H, NCH$_3$), 4.26 (q, J = 6.9 Hz, 1H, C*H*CH$_3$), 4.39 (dd, J = 9.8, 7.0 Hz, 1 H, NCHC*H*Ph), 4.70 (d, J = 9.8 Hz, 1H, NC*H*CHPh), 5.25 (dd, J = 7.0, 4.3 Hz, 1H, CHNO$_2$), 5.94 (d, J = 4.3 Hz, 1H,

NCHPh), 7.09-7.47 (10H, ArH) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 16.8 ($CHCH_3$), 31.2 (NCH_3), 54.6 (NCH*C*HPh), 56.8 (NCHPh), 64.1 (N*C*HCO), 65.1 (*C*HCH_3), 96.9 ($CHNO_2$), 125.7, 128.0, 128.5, 129.0, 129.4, 129.7, 136.6, 136.8 (ArC), 165.0 (CO), 165.1 (CO) ppm; IR (ATR) υ_{max}: 1666, 1555, 1453, 1364, 1079 cm^{-1} ;MS (EI): *m/z* 370 (M^+-NO_2, 27%),; HRMS calcd. for: $C_{21}H_{21}N_2O_3$ 370.121; found: 370.1201.

(3*R*,6*S*,7*R*,8*S*,8a*S*)-2,3-Dimethyl-7-nitro-6,8-diphenylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (22): Colorless oil (22 mg, 50% yield); $[\alpha]_D^{25}$ = 33.2 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.59 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 3.03 (s, 3H, NCH_3), 4.03 (q, *J* = 7.1 Hz, 1H, C*H*CH_3), 4.46 (dd, *J* = 9.4, 7.0 Hz, 1 H, NCHC*H*Ph), 4.68 (d, *J* = 9.4 Hz, 1H, NC*H*CHPh), 5.17 (dd, *J* = 7.0, 4.4 Hz, 1H, $CHNO_2$), 5.92 (d, *J* = 4.4 Hz, 1H, NCHPh), 7.09-7.48 (10H, ArH) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 17.4 ($CHCH_3$), 32.2 (NCH_3), 53.9 (NCH*C*HPh), 60.0 (NCHPh), 63.9 (N*C*HCO), 64.6 (*C*HCH_3), 96.7 ($CHNO_2$), 125.1, 127.9, 128.3, 128.9, 129.2, 129.7, (ArC), 164.7 (CO), 165.5 (CO) ppm; IR (ATR) υ_{max}: 1666, 1555, 1453, 1364, 1079 cm^{-1}; MS (EI): *m/z* 370 (M^+-NO_2, 27%); HRMS calcd. for: $C_{21}H_{21}N_2O_3$ 370.121; found: 370.1201.

Associated content

The Supporting Information is available free of charge on the ACS Publications website at DOI: Computational methods, details on computational calculations including energies, optimized geometries, NCI topological calculations and cartesian coordinates. Experimental details, characterization data, and NMR spectra for new compounds (PDF), computational data and X-RD analysis.

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Keywords: Michel • diastereoselective • silver • pyrazin-2-one • diketopiperazine

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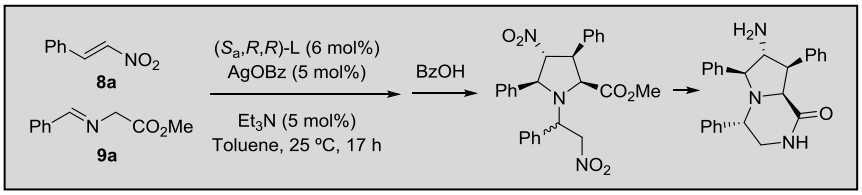

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