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One-pot synthesis of enantiopure pyrrolopiperazines

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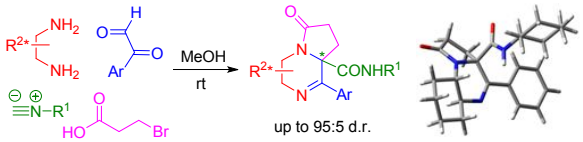
Supporting Information Placeholder

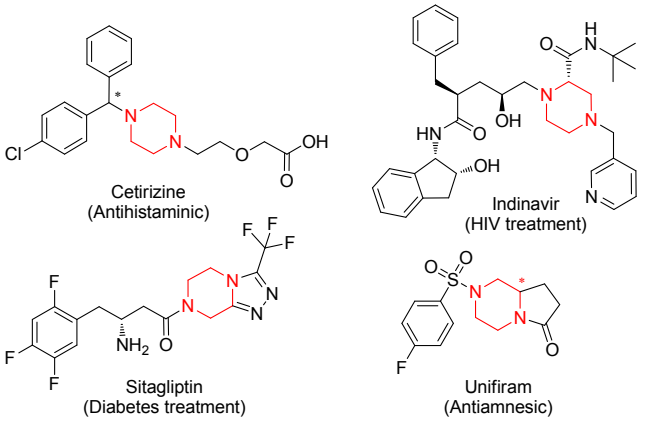


ABSTRACT: A simple one-pot protocol for the synthesis of fused pyrrolopiperazines with a complete diastereoselectivity has been developed. This novel methodology combined the Ugi reaction with a spontaneous enamine alkylation on a multicomponent domino reaction, starting from non-protected diamines and arylglyoxals.

Introduction

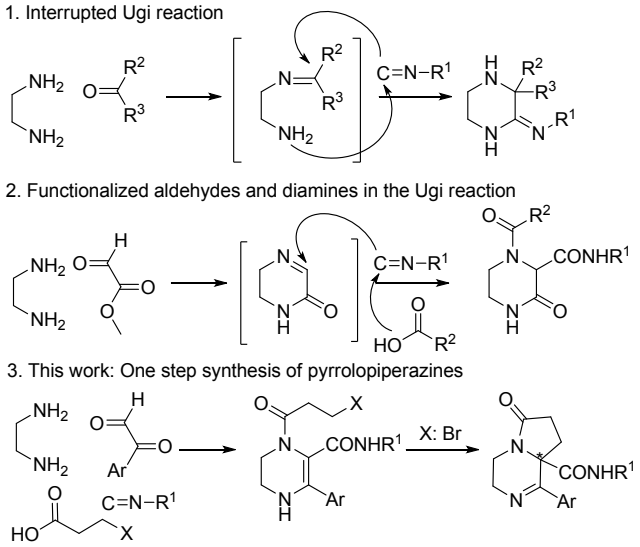
Piperazines and pyrrolopiperazines represent privileged scaffolds in medicinal chemistry. Their drug-like properties and synthetic versatility make them excellent candidates to develop ligands for diverse protein receptors in drug discovery programs.[1] Thus, these heterocyclic structures are found in many drugs and drug candidates with different pharmacological activity (Figure 1).[2] A large number of methodologies have been described for the synthesis of these heterocycles, many of them starting from non-protected 1,2-diamines, such as the reductive amination of dicarbonyl compounds,[3] the cyclocondensation with diols *via* borrowing hydrogen,[4] the reductive coupling of diimines,[5] the diamination of allenes[6] or the Michael addition-based multicomponent domino reaction involving 1,3-dicarbonyl compounds.[7]

Figure 1. Drugs containing piperazine scaffold



Within the realm of multicomponent reactions (MCR),[8] those based on the isocyanide chemistry (IMCR)[9] have demonstrated the greatest versatility in the synthesis of piperazines,[10] although the use of non-protected diamines in IMCR is rather limited. In fact, the use of non-protected primary diamines in the classical Ugi four component reaction (U-4CR) has been mainly focused in the construction of polymers[11] and macrocycles.[12] Actually, the synthesis of small molecules using diamines in the Ugi-4CR usually requires protecting groups in order to avoid competitive reactions.[13] Thus, the use of primary non-protected 1,2-diamines usually affords 2-aminopyrazines as a result of an interrupted Ugi reaction,[14] where the nitrilium ion, intermediate in the Ugi reaction, reacts intramolecularly with the second amine group of the diamine avoiding the incorporation of the carboxylic component. Furthermore, when secondary non-protected diamines are employed in the Ugi reaction, the four components are integrated in the final product with a different connectivity to the classical Ugi 4-CR adduct, the split-Ugi adduct.[15] In this case, although the carboxylic component is incorporated and the imino anhydride intermediate is generated, the expected Mumm rearrangement does not take place since the nitrogen atom involved in the Ugi reaction becomes a tertiary amine. In this situation the second secondary amine provokes the rearrangement leading to the migration of the acyl moiety to this position. For all these reasons, there are only a handful of examples of classical Ugi reaction with non-protected diamines,[16] all of them sharing a common feature, the use of functionalized aldehydes in order to block the second amine group in the first stage of the reaction. In an effort to increase the applicability of non-protected diamines in the synthesis of piperazines through the Ugi-4CR, we envisaged the combination of non-protected 1,2-diamines with arylglyoxals (Scheme 1).

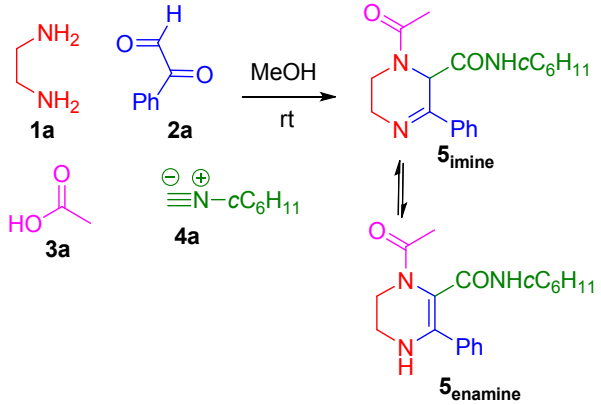
Scheme 1. Primary non-protected diamines in the Ugi reaction



Results and discussion

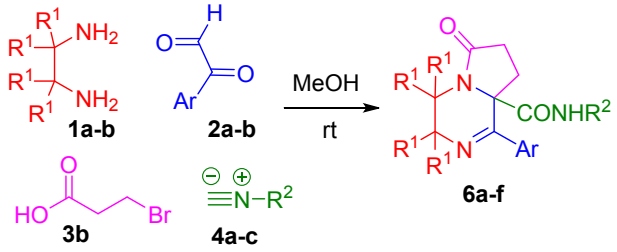
Initially, we decided to use ethylendiamine **1a**, phenylglyoxal **2a**, acetic acid **3a** and cyclohexyl isocyanide **4a** as starting reactants. The Ugi reaction was carried out under standard conditions,[17] therefore the diamine **1a** (1 equiv) was mixed with a solution of phenylglyoxal **2a** (1 equiv) in methanol. The cyclohexyl isocyanide **4a** (1 equiv) and the acetic acid **3a** (1 equiv) were then added and the mixture was stirred at room temperature for one day. After work up, the reaction mixture was analysed by NMR techniques, being the piperazine **5** the only product observed, as a mixture of imine/enamine tautomers (Scheme 2, see Supporting Information). Furthermore, the result was identical to the one obtained when we synthesized and isolated the diimine (**A** in scheme 3) from the ethylenediamine **1a** and the phenylglyoxal **2a**,[18] and then it was treated with the isocyanide **4a** and the carboxylic acid **3a**, showing that this diimine **A** was an intermediate in this synthesis.

Scheme 2. One-pot synthesis of piperazines from non-protected ethylenediamine



This result prompted us to explore the characteristic reactivity of enamines as nucleophiles,[19] introducing an electrophilic position on the carboxylic acid component in order to furnish a fused lactam with the piperazine system. We chose 3-bromopropionic acid **3b** and the reaction was carried out in the conditions described above. Gratefully, the cyclization to γ-lactam took place spontaneously,[20] yielding the corresponding pyrrolopiperazine **6a** (Table 1, Entry 1) through a multicomponent-domino reaction. In order to determine the scope of this reaction, we also used the 2,3-dimethyl-2,3-butanediamine **1b**, along with different arylglyoxals **2a-b** and isocyanides **4a-c** affording different pyrrolopiperazines **6a-f**. We observed lower yields when the hindered diamine **1b** was used (Entries 4-6 vs 1-3, Table 1).

Table 1. One-pot synthesis of pyrrolopiperazines 6 from non-protected 1,2-diamines

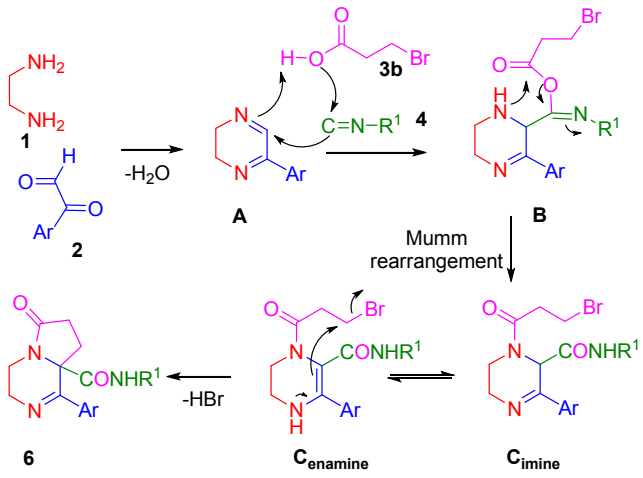


Entry	1 (R^1)	2 (Ar)	4 (R^2)	6 (%)
1	**1a** (H)	**2a** (C_6H_5)	**4a** (cC_6H_{11})	**6a** (92)
2	**1a** (H)	**2a** (C_6H_5)	**4b** (*t*Bu)	**6b** (88)
3	**1a** (H)	**2b** (4-ClC_6H_4)	**4a** (cC_6H_{11})	**6c** (89)
4	**1b** (CH_3)	**2a** (C_6H_5)	**4a** (cC_6H_{11})	**6d** (72)
5	**1b** (CH_3)	**2a** (C_6H_5)	**4b** (*t*Bu)	**6e** (58)
6	**1b** (CH_3)	**2a** (C_6H_5)	**4c** (nBu)	**6f** (68)

a. Isolated products yields

To account for this result, we proposed a mechanistic pathway starting from the cyclic diimine **A**. The complete chemoselectivity observed in the following step can be explained by the different reactivity of these imines. Thus, the Ugi reaction would take place exclusively on the aldimine, while the aromatic ketimine would remain unchanged, affording selectively the imino anhydride intermediate **B**. The Mumm rearrangement would yield the corresponding Ugi adduct, a cyclic imine $\mathbf{C}_{imine}$ in equilibrium with its tautomer, the cyclic enamine $\mathbf{C}_{enamine}$. In the last step the enamine would react spontaneously with formal HBr elimination yielding the corresponding pyrrolopiperazine **6** (Scheme 3).

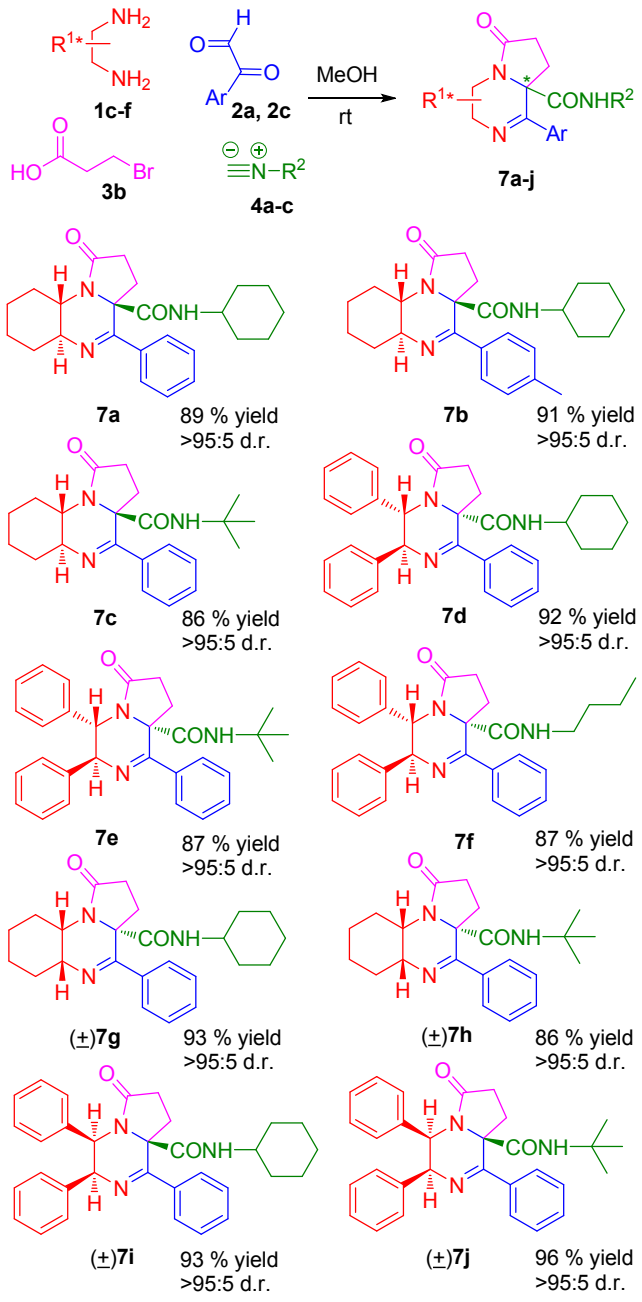
Scheme 3. Proposed mechanistic pathway



Interestingly, the new stereogenic center is created in the last cyclization step and not during the Ugi reaction.[21] This is remarkable, since the stereoselectivity achieved in the Ugi reaction is usually poor.[22] Thus, we attempted the

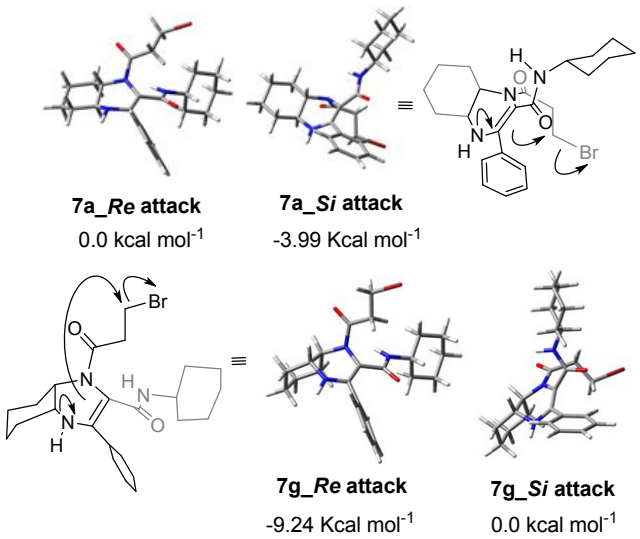
stereochemical control in the generation of the new stereogenic center by using symmetric diamine derivatives bearing chiral centres. Enantiopure diamines, (1S,2S)-1,2-cyclohexanediamine **1c** and (1S,2S)-1,2-diphenylethylenediamine **1d**, and *meso*-diamines, *cis*-diaminocyclohexane **1e** and *meso*-1,2-diphenylethylenediamine **1f** were assayed employing the same protocol described above, and the corresponding pyrrolopiperazines **7a-j** were obtained with total diastereoselectivity in excellent yields, regardless of the nature of the diamine employed (Scheme 4). The configuration of the new stereogenic centers was determined by NOESY experiments. Moreover, structural analyses by X-ray diffraction of compounds **7a**[23] and **7g** confirmed the determined stereochemistry (see Supporting Information).

Scheme 4. One-pot diastereoselective synthesis of pyrrolopyrazines 7



The complete diastereoselectivity observed in the last cyclization step was also studied computationally. This result can be explained by the reaction through the preferred conformations in the cyclic enamine intermediate, determined by DFT calculations using Gaussian 09.[24] Thus, in the synthesis of **7a**, the most stable conformation of the enamine intermediate favors the *Si* face attack of the enamine, while for the synthesis of **7d**, **7g** and **7i** the preferred conformation favors the *Re* face attack (Figure 2, see Supporting Information).

Figure 2. Energies calculated (in gas phase) for the most stable conformations of the enamine intermediate in the synthesis of 7a and 7g



Conclusion

In this work we have developed an efficient and simple methodology for the synthesis of enantiopure pyrrolopiperazines through a multicomponent domino reaction, Ugi/enamine alkylation, using non-protected diamines in a one-pot sequence with high yield, and total diastereoselectivity when diamines bearing stereogenic centers are used.

Experimental section

General methods. Melting points are not corrected. Optical rotations were measured on a Zeiss D-7082 Polarimeter in a 1 dm cell and concentrations are given in g/100 ml. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, on a Varian Mercury 300 system, DEPT-135 experiments were conducted to assign carbon-13 signals. Chemical shifts are reported in parts per million with respect to residual solvent protons, and coupling constants are reported in hertz. High resolution mass spectra were recorded in on a 6545 Q-TOF Agilent LC-MS mass spectrometer (positive electrospray ionization mode, ESI (+)).

General procedure for the synthesis of pyrrolopiperazines 6 and 7. The corresponding diamine **1a-d** (1 mmol) was added to a solution of arylglyoxal **2a-c** (1 mmol) in methanol (10 ml). The solution was stirred for 10 min at room temperature. Then the 3-bromopropionic acid **3b** (1 mmol) and the isocyanide **2a-b** (1 mmol) were added to the solution and the mixture was stirred for 24 h. Then the solvent was removed and the residue was dissolved in dichloromethane and washed first with 10%

aqueous HCl solution, and then with saturated aqueous Na_2CO_3 solution. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by column chromatography.

N-Cyclohexyl-6-oxo-1-phenyl-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carboxamide ***(6a)***.White solid (Hexane/AcOEt, 2:1). Yield: 312 mg, 92 %. M. p. 158-160 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70-7.66 (m, 2H), 7.37-7.30 (m, 3H), 6.00 (d, *J* = 8.3 Hz, 1H), 3.99-3.72 (m, 4H), 3.23-3.13 (m, 1H), 2.86-2.67 (m, 2H), 2.27-2.19 (m, 1H), 1.94-0.93 (m, 11H). ^{13}C{^{1}H} NMR (75MHz, $CDCl_3$) δ: 173.3 (Cq), 168.1 (Cq), 166.5 (Cq), 135.8 (Cq), 130.4 (CH_{Ar}), 128.4 (CH_{Ar}), 127.6 (CH_{Ar}), 66.6 (Cq), 49.4 (CH), 47.5 (CH_2), 34.4 (CH_2), 32.8 (CH_2), 32.4 (CH_2), 30.7 (CH_2), 29.9 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 24.7 (CH_2). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{26}N_3O_2$ 340.2020; Found 340.2022

N-(tert-Butyl)-6-oxo-1-phenyl-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carboxamide. ***(6b)***. Brown solid (Hexane/AcOEt, 2:1). Yield: 275 mg, 88 %. M. p. 106-108 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.63 (m, 2H), 7.43-7.31 (m, 3H), 5.52 (s, 1H), 4.10-3.94 (m, 2H), 3.91-3.80 (m, 1H), 3.26-3.12 (m, 1H), 2.91-2.70 (m, 2H), 2.35-2.11 (m, 1H), 1.94-1.82 (m, 1H), 1.28 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.3 (Cq), 168.1 (Cq), 166.2 (Cq), 135.6 (Cq), 130.5 (CH_{Ar}), 128.5 (CH_{Ar}), 127.5 (CH_{Ar}), 67.2 (Cq), 52.5 (Cq), 47.7 (CH_2), 34.3 (CH_2), 30.8 (CH_2), 29.6 (CH_2), 28.4 (CH_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{24}N_3O_2$ 314.1863; Found 314.1866.

1-(4-Chlorophenyl)-N-cyclohexyl-6-oxo-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carboxamide (***6c***). White solid (Hexane/AcOEt, 2:1). Yield 332 mg, 89 %. M. p. 188-190 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 5.84 (d, *J* = 8.2 Hz, 1H), 4.06-3.67 (m, 4H), 3.33-3.11 (m, 1H), 2.95-2.65 (m, 2H), 2.42-2.18 (m, 1H), 2.10-0.81 (m, 11H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.4 (Cq), 167.9 (Cq), 165.8 (Cq), 136.7 (Cq), 134.2 (Cq), 129.1 (CH_{Ar}), 128.6 (CH_{Ar}), 66.6 (Cq), 49.4 (CH), 47.5 (CH_2), 34.6 (CH_2), 32.9 (CH_2), 32.5 (CH_2), 30.6 (CH_2), 29.9 (CH_2), 25.2 (CH_2), 24.8 (CH_2), 24.7 (CH_2). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{25}ClN_3O_2$ 374.1630; Found 374.1632.

N-Cyclohexyl-3,3,4,4-tetramethyl-6-oxo-1-phenyl-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carboxamide ***(6d)***. Orange solid (Hexane/AcOEt, 3:1). Yield 284 mg, 72 %. M. p. 181-182 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.79 (m, 2H), 7.40-7.38 (m, 3H), 5.92 (d, *J* = 8.2 Hz, 1H), 3.89-3.57 (m, 1H), 2.65 (ddd, *J* = 16.5, 12.3, 8.4 Hz, 1H), 2.48 (dd, *J* = 12.7, 8.4 Hz, 1H), 2.24 (dd, *J* = 16.5, 9.3 Hz, 1H), 2.01 (td, *J* = 12.3, 9.3 Hz, 1H), 1.86-1.77 (m, 3H), 1.54 (s, 3H), 1.50 (s, 3H), 1.39 (s, 3H), 1.23 (s, 3H), 1.63-1.02 (m, 7H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 176.1 (Cq), 170.7 (Cq), 137.9 (Cq), 129.7 (CH_{Ar}), 128.9 (CH_{Ar}), 128.4 (CH_{Ar}), 67.9 (Cq), 61.9 (Cq), 59.9 (Cq), 48.7 (CH), 33.6 (CH_2), 32.7 (CH_2), 32.1 (CH_2), 31.1 (CH_2), 27.3 (CH_3), 25.3 (CH_2), 24.6 (CH_2), 23.7 (CH_3), 22.8 (CH_3), 21.8 (CH_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{34}N_3O_2$ 396.2646; Found 396.2658.

*N-(tert-Butyl)-3,3,4,4-tetramethyl-6-oxo-1-phenyl-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carbo*xamide (6e). Pale orange solid (Hexane/AcOEt, 5:1). Yield 214 mg, 58 %. M. p. 148-150 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.85 (m, 2H), 7.42-7.40 (m, 3H), 5.78 (s, 1H), 2.72-2.59 (m, 1H), 2.49 (dd, *J* = 12.5, 8.4 Hz, 1H), 2.26 (dd, *J* = 16.5, 9.5 Hz, 1H), 2.09-1.98 (m, 1H), 1.52 (s, 6H), 1.39 (s, 3H), 1.27 (s, 3H), 1.26 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 175.8 (Cq), 170.5 (Cq), 138.1 (Cq), 129.8 (CH_{Ar}), 128.9 (CH_{Ar}), 128.5 (CH_{Ar}), 61.9 (Cq), 59.8 (Cq), 51.8 (Cq), 33.5 (CH_2), 31.2 (CH_2), 28.2 (CH_3), 27.2 (CH_3), 23.8 (CH_3), 22.8 (CH_3), 21.8 (CH_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{32}N_3O_2$ 370.2489; Found 370.2499.

N-Butyl-3,3,4,4-tetramethyl-6-oxo-1-phenyl-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carboxamide ***(6f)***. Orange solid (Hexane/AcOEt, 3:1). Yield 251 mg, 68 %. M. p. 149-150 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93-7.81 (m, 2H), 7.40-7.31 (m, 3H), 6.28 (t, *J* = 5.7 Hz, 1H), 3.55-3.04 (m, 2H), 2.66 (ddd, *J* = 16.6, 12.7, 8.4 Hz, 1H), 2.46 (dd, *J* = 12.7, 8.7 Hz, 1H), 2.22 (dd, *J* = 16.6, 9.9 Hz, 1H), 2.07-1.90 (m, 1H), 1.55 (s, 3H), 1.47 (s, 3H), 1.45-1.40 (m, 2H), 1.39 (s, 3H), 1.31-1.22 (m, 2H), 1.20 (s, 3H), 0.87 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 176.2 (Cq), 171.8 (Cq), 165.6 (Cq), 138.0 (Cq), 129.6 (CH_{Ar}), 128.9 (CH_{Ar}), 128.3 (CH_{Ar}), 67.9 (Cq), 61.8 (Cq), 60.0 (Cq), 39.9 (CH_2), 33.5 (CH_2), 31.1 (CH_2), 30.9 (CH_2), 27.4 (CH_3), 23.5 (CH_3), 22.8 (CH_3), 21.8 (CH_3), 20.1 (CH_2), 13.6 (CH_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{32}N_3O_2$ 370.2489; Found 370.2498.

(3aR,5aS,9aS)-N-Cyclohexyl-1-oxo-4-phenyl-1,2,3,3a,5a,6,7,8,9,9a-decahydropyrrolo[1,2-a]quinoxaline-3a-carboxamide ***(7a)***. Brown solid. (Hexane/AcOEt, 2:1). Yield 350 mg, 89 %. M. p. 158-160 ºC. $[\alpha]_D$ = +148.9º (c = 1.41, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69 (d, *J* = 7.4 Hz, 2H), 7.44-7.34 (m, 3H), 5.56 (d, *J* = 8.4 Hz, 1H), 3.90-3.81 (m, 1H), 3.41 (ddd, *J* = 12.2, 9.8, 3.7 Hz, 1H), 3.14 (ddd, *J* = 13.0, 9.8, 3.6 Hz, 1H), 2.92-2.64 (m, 4H), 2.46-2.23 (m, 4H), 1.94-0.93 (m, 14H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 173.7 (Cq), 168.5 (Cq), 163.5 (Cq), 136.0 (Cq), 130.6 (CH_{Ar}), 128.5 (CH_{Ar}), 127.9 (CH_{Ar}), 70.3 (Cq), 63.1 (CH), 57.3 (CH), 49.1 (CH), 33.8 (CH_2), 33.0 (CH_2), 32.3 (CH_2), 29.2 (CH_2), 28.1 (CH_2), 26.0 (CH_2), 25.5 (CH_2), 25.2 (CH_2), 24.6 (CH_2), 24.4 (CH_2). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{32}N_3O_2$ 394.2489; Found 394.2492.

(3aR,5aS,9aS)-N-Cyclohexyl-1-oxo-4-(p-tolyl)-1,2,3,3a,5a,6,7,8,9,9a-decahydropyrrolo[1,2-a]quinoxaline-3a-carboxamide ***(7b)***. Yellow solid. (Hexane/AcOEt, 2:1). Yield 370 mg, 91 %. M. p. 69-71 ºC. $[\alpha]_D$ = +123.6º (c = 1.11, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 5.55 (d, *J* = 8.2 Hz, 1H), 3.87-3.77 (m, 1H), 3.36 (ddd, *J* = 12.7, 9.9, 3.7 Hz, 1H), 3.09 (ddd, *J* = 13.0, 9.9, 3.5, 1H), 2.89-2.60 (m, 4H), 2.33 (s, 3H), 2.43-2.18 (m, 4H), 1.92-0.87 (m, 14H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 173.6 (Cq), 168.6 (Cq), 163.1 (Cq), 140.7 (Cq), 132.9 (Cq), 129.1 (CH_{Ar}), 127.8 (CH_{Ar}), 70.2 (Cq), 63.0 (CH), 57.2 (CH), 49.0 (CH), 33.8 (CH_2), 32.8 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 29.2 (CH_2), 28.1 (CH_2), 26.0 (CH_2), 25.5 (CH_2), 25.2 (CH_2), 24.6 (CH_2), 24.4 (CH_2), 21.2 (CH_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{34}N_3O_2$ 408.2646; Found 408.2648.

(3aR,5aS,9aS)-N-(tert-Butyl)-4-phenyl-1-oxo-1,2,3,3a,5a,6,7,8,9,9a-decahydropyrrolo[1,2-a]quinoxaline-3a-carboxamide ***(7c)***. Yellow sticky solid. (Hexane/AcOEt, 2:1). Yield 316 mg, 86 %. $[\alpha]_D$ = +161.4º (c = 0.95, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69-7.65 (m, 2H), 7.42-7.33 (m, 3H), 5.40 (s, 1H), 3.39 (ddd, *J* = 12.6, 9.5, 3.5 Hz,1H), 3.14 (ddd, *J* = 12.7, 9.5, 3.4 Hz, 1H), 2.87-2.63 (m, 3H), 2.45-2.20 (m, 3H), 1.94-1.78 (m, 3H), 1.52-1.17 (m, 3H), 1.27 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 173.7 (Cq), 168.6 (Cq), 163.6 (Cq), 135.8 (Cq), 130.5 (CH_{Ar}), 128.6 (CH_{Ar}), 127.9 (CH_{Ar}), 71.0 (Cq), 63.2 (CH), 57.3 (CH), 52.5 (Cq), 33.9 (CH_2), 32.3 (CH_2), 29.2 (CH_2), 28.5 (CH_3), 28.2 (CH_2), 26.2 (CH_2),

25.6 (CH_2). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{30}N_3O_2$ 368.2333; Found 368.2345.

(3S,4S,8aS)-N-Cyclohexyl-6-oxo-1,3,4-triphenyl-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carboxamide (***7d***). Yellow solid (Hexane/AcOEt, 3:1). Yield 452 mg, 92 %. M. p. 60-62 ºC. $[\alpha]_D$ = -95.4º (c = 0.49, CH_3OH).^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.85-7.81 (m, 2H), 7.48-7.42 (m, 3H) 7.27-7.21 (m, 8H), 7.11-7.07 (m, 2H), 5.74 (d, *J* = 7.9 Hz, 1H), 4.94 (d, *J* = 8.6 Hz, 1H), 4.80 (d, *J* = 8.6 Hz, 1H), 3.82-3.70 (m, 1H), 2.98-2.70 (m, 2H), 2.38-2.19 (m, 2H), 1.92-0.82 (m, 10H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 175.3 (Cq), 171.6 (Cq), 169.5 (Cq), 140.1 (Cq), 138.3 (Cq), 136.5 (Cq), 130.5 (CH_{Ar}), 128.6 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 128.0 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 67.3 (Cq), 65.7 (CH), 59.7 (CH), 49.2 (CH), 32.5 (CH_2), 32.4 (CH_2), 32.3 (CH_2), 30.2 (CH_2), 29.7 (CH_2), 25.2 (CH_2), 24.7 (CH_2), 24.6 (CH_2). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{32}H_{34}N_3O_2$ 492.2646; Found 492.2653.

*(3S,4S,8aS)-N-(tert-Butyl)-6-oxo-1,3,4-triphenyl-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carboxamide (**7e**).* Red solid. (Hexane/AcOEt, 4:1). Yield 404 mg, 87 %. M. p. 56-58 ºC. $[\alpha]_D$ = -105.4º (c = 0.57, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87-7.83 (m, 2H), 7.48-7.45 (m, 3H), 7.33-7.23 (m, 8H), 7.14-7.10 (m, 2H), 5.60 (s, 1H), 5.02 (d, *J* = 8.3 Hz, 1H), 4.88 (d, *J* = 8.3 Hz, 1H), 2.92-2.64 (m, 2H), 2.40-2.18 (m, 2H), 1.23 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 175.5 (Cq), 171.4 (Cq), 169.4 (Cq), 140.0 (Cq), 138.5 (Cq), 136.6 (Cq), 130.5 (CH_{Ar}), 128.5 (CH_{Ar}), 128.5 (CH_{Ar}), 128.3 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 67.8 (Cq), 65.1 (CH), 59.2 (CH), 52.1 (Cq), 32.3 (CH_2), 30.2 (CH_2), 28.2 (CH_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{30}H_{32}N_3O_2$ 466.2489; Found 466.2496

*(3S,4S,8aS)-N-Butyl-6-oxo-1,3,4-triphenyl-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carboxamide (**7f**).* Yellow solid. (Hexane/AcOEt, 5:1). Yield 274 mg, 59 %. M. p. 141-143 ºC. $[\alpha]_D$ = -51.4º (c = 0.44, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.78 (m, 2H), 7.50-7.38 (m, 3H), 7.36-7.22 (m, 8H), 7.18-7.05 (m, 2H), 5.62 (t, *J* = 5.7 Hz, 1H), 5.21 (d, *J* = 7.1 Hz, 1H), 4.98 (d, *J* = 7.1 Hz, 1H), 3.14 (td, *J* = 13.2, 7.1 Hz, 1H), 2.98-2.78 (m, 3H), 2.30-2.20 (m, 2H), 1.36-1.04 (m, 4H), 0.83 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 175.1 (Cq), 170.1 (Cq), 140.0 (Cq), 138.3 (Cq), 136.1 (Cq), 130.7 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 66.7 (Cq), 64.5 (CH), 58.5 (CH), 39.9 (CH_2), 32.1 (CH_2), 30.9 (CH_2), 30.3 (CH_2), 20.0 (CH_2), 13.6 (CH_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{30}H_{32}N_3O_2$ 466.2489; Found 466.2504.

(3aR,5aS*,9aR*)-N-Cyclohexyl-1-oxo-4-phenyl-1,2,3,3a,5a,6,7,8,9,9a-decahydropyrrolo[1,2-a]quinoxaline-3a-carboxamide (**7g**).* Pale yellow solid. (Hexane/AcOEt, 3:1). Yield 365 mg, 93 %. M. p. 156-158 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (dd, J = 7.6, 2.0 Hz, 2H), 7.47-7.38 (m, 3H), 5.61 (d, J = 8.2 Hz, 1H), 4.43-4.25 (m, 1H), 3.72-3.39 (m, 2H), 3.00-2.77 (m, 2H), 2.48-2.31 (m, 3H), 1.88-0.81 (m, 17H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 174.8 (Cq), 169.2 (Cq), 163.9 (Cq), 138.3 (Cq), 130.1 (CH_{Ar}), 128.4 (CH_{Ar}), 128.0 (CH_{Ar}), 66.3 (Cq), 56.6 (CH), 48.6 (CH), 46.7 (CH), 33.8 (CH_2), 32.4 (CH_2), 32.3 (CH_2), 32.2 (CH_2), 31.2 (CH_2), 25.8 (CH_2), 25.3 (CH_2), 24.6 (CH_2), 24.4 (CH_2), 20.7 (CH_2). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{31}NaN_3O_2$ 416.2308; Found 416.2312.

(3aR,5aS*,9aR*)-N-(tert-Butyl)-1-oxo-4-phenyl-1,2,3,3a,5a,6,7,8,9,9a-decahydropyrrolo[1,2-a]quinoxaline-3a-carboxamide (**7h**).* White solid. (Hexane/AcOEt, 3:1). Yield 315 mg, 86 %. M. p. 102-104 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.76-7.73 (m, 2H), 7.46-7.40 (m, 3H), 5.49 (s, 1H), 4.38-4.30 (m, 1H), 3.72-3.68 (m, 1H), 2.97-2.81 (m, 2H), 2.46-2.23 (m, 3H), 1.88-0.96 (m, 7H), 1.12 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 174.6 (Cq), 168.9 (Cq), 163.7 (Cq), 137.8 (Cq), 130.1 (CH_{Ar}), 128.4 (CH_{Ar}), 127.8 (CH_{Ar}), 66.7 (Cq), 56.5 (CH), 51.5 (Cq), 46.5 (CH), 33.5 (CH_2), 32.3 (CH_2), 31.0 (CH_2), 21.9 (CH_3), 25.7 (CH_2), 24.5 (CH_2), 20.6 (CH_2). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{29}NaN_3O_2$ 390.2152; Found 390.2156.

(3R,4S*,8aS*)-N-Cyclohexyl-6-oxo-1,3,4-triphenyl-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carboxamide (**7i**).* Orange solid. (Hexane/AcOEt, 3:1). Yield 457 mg, 93 %. M. p. 144-145 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.91 (m, 2H), 7.78-7.75 (m, 2H), 7.45-7.12 (m, 11H), 6.28 (d, *J* = 5.5 Hz, 1H), 5.15 (d, *J* = 5.5 Hz, 1H), 4.45 (d, *J* = 7.7 Hz, 1H), 3.43 (dd, *J* = 11.9, 7.8 Hz, 1H), 3.09-2.93 (m, 2H), 2.53 (dd, *J* = 16.5, 8.8 Hz, 1H), 2.28 (td, *J* = 11.9, 8.8 Hz, 1H), 1.37-0.76 (m, 8H), 0.21-0.07 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 176.2 (Cq), 167.2 (Cq), 163.5 (Cq), 140.0 (Cq), 137.1 (Cq), 135.1 (Cq), 130.5 (CH_{Ar}), 130.4 (CH_{Ar}), 128.9 (CH_{Ar}), 128.5 (CH_{Ar}), 128.3 (CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (CH_{Ar}), 126.8 (CH_{Ar}), 126.4 (CH_{Ar}), 67.2 (Cq), 61.3 (CH), 52.4 (CH), 48.5 (CH), 34.3 (CH_2), 31.5 (CH_2), 31.2 (CH_2), 25.2 (CH_2), 24.5 (CH_2), 24.4 (CH_2). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{32}H_{34}N_3O_2$ 492.2646; Found 492.2655.

(3R,4S*,8aS*)-N-(tert-Butyl)-6-oxo-1,3,4-triphenyl-3,4,6,7,8,8a-hexahydropyrrolo[1,2-a]pyrazine-8a-carboxamide* (**7j**). Pale yellow solid. (Hexane/AcOEt, 3:1). Yield 446 mg, 96 %. M. p. 194-195 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.93 (m, 2H), 7.80-7.77 (m, 2H), 7.46-7.12 (m, 11H), 6.30 (d, *J* = 5.5 Hz, 1H), 5.15 (d, *J* = 5.5 Hz, 1H), 4.37 (s, 1H, NH), 3.39 (dd, *J* = 11.9, 8.0 Hz, 1H), 3.11 (ddd, *J* = 16.5, 11.9, 8.0 Hz, 1H), 2.54 (dd, *J* = 16.5, 9.0 Hz, 1H), 2.24 (td, *J* = 11.9, 9.0 Hz, 1H), 0.60 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 176.4 (Cq), 167.3 (Cq), 163.5 (Cq), 140.1 (Cq), 136.9 (Cq), 135.2 (Cq), 130.5 (CH_{Ar}), 128.9 (CH_{Ar}), 128.5 (CH_{Ar}), 128.3 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 126.8 (CH_{Ar}), 126.3 (CH_{Ar}), 67.4 (Cq), 61.3 (CH), 52.2 (CH), 51.0 (Cq), 34.3 (CH_2), 31.7 (CH_2), 27.3 (CH_3). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{30}H_{32}N_3O_2$ 466.2489; Found 466.2498.

Computational studies. The geometries of all species were fully optimized at the B3LYP/6-31G** level. The nature of all optimized structures was determined using harmonic frequency analysis as true minima with no imaginary frequencies. All calculations were performed using the Gaussian 09 program.[24]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of ^{1}H NMR, ^{13}C NMR and high-resolution mass spectra, and computational data (PDF).

X-ray chrystallographic data for compounds **7a** and **7g** (CIF). CCDC 1982178-1982179

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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