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Microwave-Assisted Stereoselective One-Pot Synthesis of Symmetrical and Unsymmetrical 2,5-Diketopiperazines from Unprotected Amino Acids

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In memory of Professor Ivar K. Ugi (1930–2005)

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The facile condensation of unprotected amino acids by a phosphite-promoted one-step coupling reaction is a highly efficient synthesis to generate stereoselective and optically pure symmetrical and unsymmetrical functionalized diketopiperazines. The use of microwaves enhanced by small amounts of ionic liquid is accompanied by significant improvement in reaction times and yields. Simple filtration through a pad of silica provides the pure compounds in very good to excellent yields.

Introduction

In nature, amino acids can be found in a great variety. Their role for life existence is indisputable. Therefore, the smallest cyclic peptides, the diketopiperazines and their higher-functionalized analogues, the epithiodiketopiperazines, are common motifs that can be found in several natural products (Figure 1).[1–4]

In recent research, the 2,5-diketopiperazines have become more attractive due to their diverse biological properties,[5] such as antitumor,[6,7] antiviral,[8] antifungal,[9,10] antibacterial[11,12] or antifouling[13] activities. They are also used as organic catalysts for the hydrocyanation of imines.[14] Diketopiperazines are also jointly responsible for the bitter taste in some food like coffee, beer, cacao and chocolate.[15]

In the past few years, using microwave energy for chemical reactions has become increasingly popular in organic chemistry.[16] Since the first reports of microwave-assisted synthesis in 1986,[17,18] microwave technology has matured to an established technique, and the efficiency of microwave flash heating, with often dramatically reduced reaction times, is just one of the many advantages. Both mechanisms—dipolar polarization and conduction—are responsible for the heating effect. To solve problems in heating with apolar solvents like hexane or toluene, power modulators

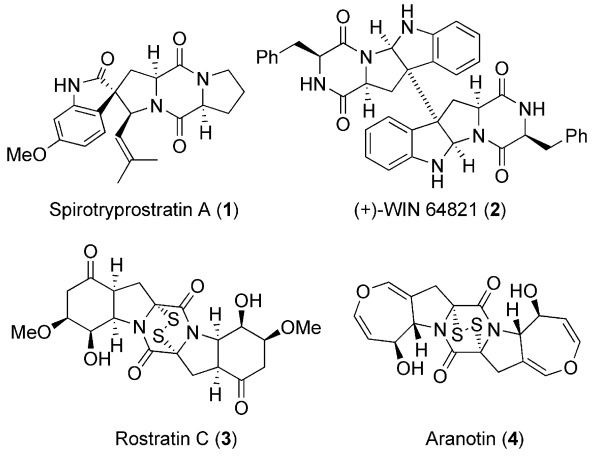

Figure 1. Natural 2,5-diketo- and epithiodiketopiperazines.

such as charcoal, silicon carbide,[19] palladium salts or ionic liquids can be added. Ionic liquids are thermally stable salts with melting points below 100 °C. They consist of a bulky organic cation and an inorganic or organic anion. These compounds can be used as catalysts (including chiral catalysts) or solvents for many organic reactions. Ionic liquids as solvents are nontoxic, inflammable and many times recyclable. Ionic liquids combined with microwave irradiation form a new synergy in organic chemistry and have potential in a huge variety of applications. One example of these new applications is presented in this article.

On our way towards the cytotoxic compound Rostratin C (**3**), we were faced with two challenges. The first challenge was the synthesis of the necessary monomer, the bicyclic

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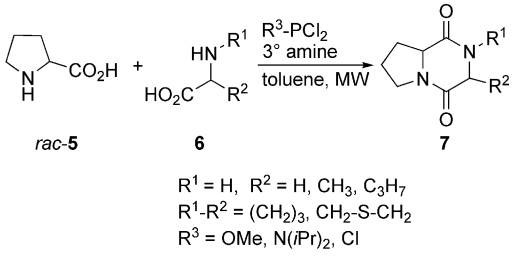
amino acid, whose skeleton was accessible via intramolecular Diels–Alder reaction.[20] The second challenge was an efficient method for the condensation of amino acids.

To avoid the often-published multi-step synthesis containing standard peptide chemistry, with its protecting group, activation and coupling strategies,[21] we used a phosphorus-promoted coupling method with microwave irradiation-induced heating (Scheme 1).[22] Of course, there exist a lot of other synthetic pathways for a brief access to 2,5-diketopierazines, e.g. thermal cycloamidation[23] or vaporous condensation[24] of sublimated amino acids under reduced pressure in the presence of silica. The yields of diketopiperazines prepared in this manner are comparable, but the substrate scope is limited to the thermal stability of the used α-amino acids and the stereoselectivity is not consistent. In contrast to these methods, the procedure described herein is gentler and uses fraction of the time, energy and physical complexity of previous methods. In preliminary experiments, we tried to condense protected amino acids using boronic acids[25] with limited success. Thus, we switched to the phosphorus-promoted coupling of unprotected amino acids.

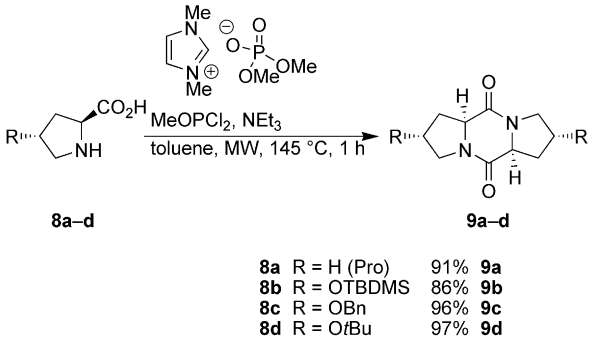


Scheme 1. P^{III}-promoted coupling of amino acids.

Results and Discussion

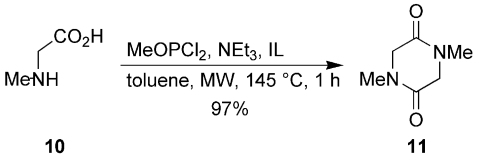
The condensation occurs by prolonged heating of amino acids together with methyldichlorophosphite in the presence of excess triethylamine. The reaction takes place between 70 and 150 °C; thus toluene, having a boiling point of about 111 °C, was chosen as the solvent. However, due to its low loss factor [tanδ = 0.040 (2.45 GHz; 20 °C)],[26] toluene is more or less transparent to microwave irradiation. To enhance the efficiency of absorption, along with a rapid heating of the solvent, small amounts of ionic liquid were added.[27] The ionic liquid should be very similar to other reactants used in order to avoid difficulties with these high-boiling substances. Thus, we chose 1,3-dimethylimidazolium dimethyl phosphate, because the imidazolium cation is similar to the nitrogen base, and the phosphate anion is very close to the coupling promoter. The ionic liquid was easily and quantitatively removed by filtration together with the accumulated ammonium salts. During the optimization of this method, charcoal was also used as a power modulator, with comparable yields, but with more difficulty in the work-up.

Starting with the cyclization of proline (**8a**), we could directly isolate the tricyclic product **9a** in good yield and very good purity. The compatibility of protected functional groups was proven by the coupling of protected 4-*trans*-hydroxyprolines. We decided to use the well-established and base-stable silyl, benzyl and alkyl ethers **9b**–**d**. In all cases, reaction occurred without noteworthy difficulties in good yields (Scheme 2). These results show the applicability of this method in the total synthesis of natural products.



Scheme 2. Synthesis of cyclo(Pro-Pro) and substituted derivatives.

This method is also applicable in condensing the well-known primary natural amino acids, which has already been shown by Ugi and Scheeser.[22] To avoid the additional step of protecting the free amide functionalities in following reactions, we used sarcosine (**10**), the naturally occurring *N*-methylglycine, to generate a derivative of the smallest possible cyclic dipeptide **11**, in excellent yield (Scheme 3). Furthermore, the +I-effect of the additional methyl group increases the nucleophilic character of the nitrogen atom, and so has a positive influence on the coupling.



Scheme 3. Dimerization of sarcosine (**10**).

With these optimized reaction conditions, we tried to find out what happens to amino acids with sp^2-hybridization or quaternary stereogenic centers. Thus, we coupled 2-pyrrolecarboxylic acid, 2-indolecarboxylic acid and (*S*)-2-methylproline to form their corresponding 2,5-diketopiperazines **12**–**14**, in satisfactory yields (Figure 2).

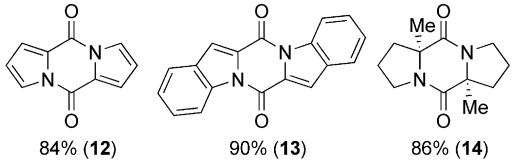


Figure 2. 2,5-Diketopiperazines from sterically hindered amino acids.

With regard to the target molecules Rostratin C (**3**) and Aranotin (**4**), our main interest is in polycyclic ring systems like the structure of **13**. Condensation of the partially saturated indole derivatives indoline- and octahydroindolecar-

boxylic acid, afforded the corresponding pentacyclic 2,5-diketopiperazines **15** and **16** in 93% and 97% yield, respectively (Figure 3).

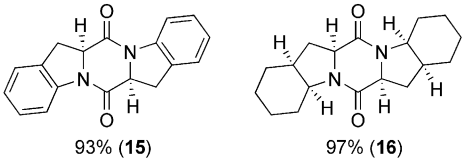


Figure 3. Pentacyclic diketopiperazines **15** and **16**.

Due to the importance of this structural motif in natural product synthesis, we were also interested in an extension of this one-pot reaction to unsymmetrical 2,5-diketopiperazines. There are few other methods which afford such defined heterodiketopiperazines in a single step, with excellent yields.[28] To comply with this challenge, we synthesized all possible cross-coupled permutations **17**–**22** using the highly reactive proline (**8a**), sarcosine (**10**), indoline- and octahydroindolecarboxylic acids, in overall good yields (Figure 4).

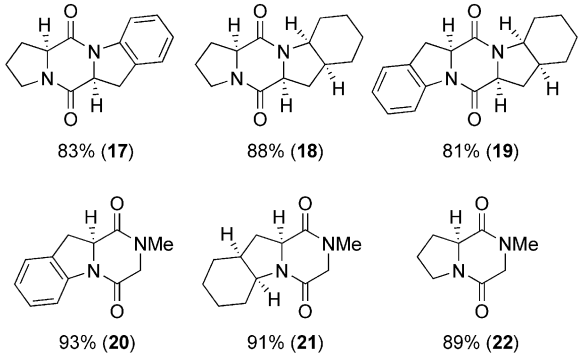


Figure 4. Unsymmetrical 2,5-diketopiperazines **17**–**22**.

To obtain the heterodiketopiperazines without any byproducts, especially not the corresponding homodiketopiperazines, a small excess of about 1.2 equiv. of one amino acid was necessary. In contrast to the C_2-symmetrical homodiketopiperazines, the unsymmetrical heterocycles have an increased solubility in most organic solvents. With respect to the order of the used amino acids, no significant differences in yields could be detected in initial cross-coupling experiments.

Due to the mild reaction conditions, racemization or inversion of the stereogenic centres of the amino acids was neither expected nor ascertained. In all cases, complete retention of the stereochemistry was observed by NMR spectroscopy. Furthermore, this issue could be unequivocally proven by X-ray crystallography of **11**, **12** and **14** (Figures 5, 6 and 7).

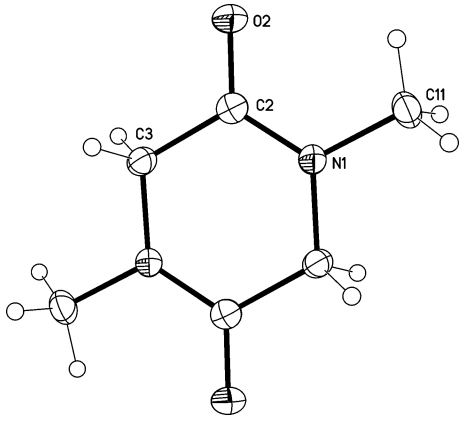


Figure 5. Molecular structure of **11**. Displacement parameters are drawn at 50% probability level. The molecule possesses crystallographic C_i symmetry.

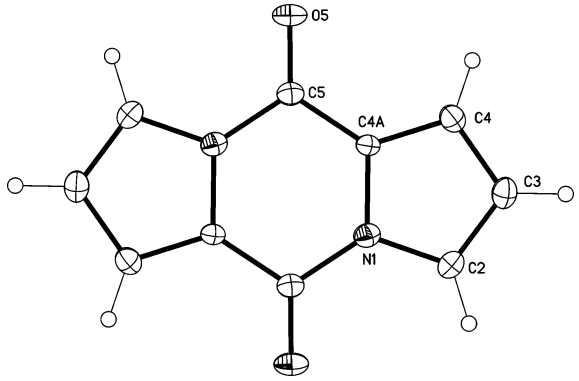


Figure 6. Molecular structure of **12**. Displacement parameters are drawn at 50% probability level. The molecule possesses crystallographic C_i symmetry.

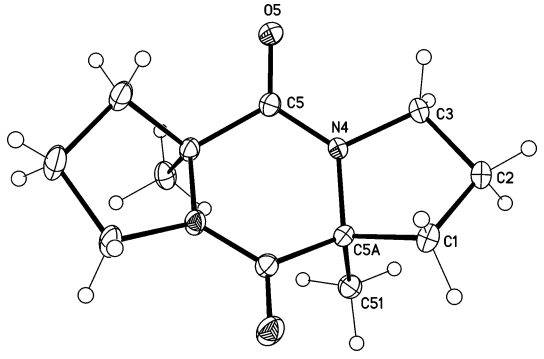


Figure 7. Molecular structure of **14**. Displacement parameters are drawn at 50% probability level. The molecule possesses crystallographic C_2 symmetry.

Conclusions

Within this article we describe a convenient route to obtain highly functionalized symmetrical and unsymmetrical 2,5-diketopiperazines in a single-step, one-pot reaction. This method is characterized by overall good yields, scalability and tolerance to most popular base-stable protecting groups. Another advantage of this reaction is its very simple work-up, consisting in a facile filtration step that removes the ammonium salts and the ionic liquid quantitatively. Furthermore, it was shown that the reaction is free of racemization or inversion, and leads reliably and successfully to the expected 2,5-diketopiperazines without any byproducts.

Experimental Section

General Remarks: Solvents and chemicals used for reactions were purchased from commercial suppliers. Solvents were dried under standard conditions; chemicals were used without further purification. All reactions were carried out under Ar in flame-dried glassware. Evaporation of solvents and concentration of reaction mixtures were performed in vacuo at 40 °C on a Büchi rotary evaporator. TLC was performed on silica gel plates (Kieselgel 60, F_{254}, Merck) with detection by UV and visualization by spraying with the Seebach solution.[29] Normal-phase silica gel (silica gel 60, 230–400 mesh, Merck) was used for preparative chromatography. Solvents used were hexane and ethyl acetate (EE). Melting points (m.p.) were determined with a Laboratory Devices Inc. Mel-Temp II and are uncorrected. IR spectra were recorded with a Bruker IFS88. Absorption is reported as ν values in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker AC-250, AM-400 or DRX 500. Chemical shifts are reported as δ values (ppm) downfield from internal TMS in the indicated solvent. Coupling constants (J) are given in Hz; ^1H: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, ^{13}C: p = primary C, s = secondary C, t = tertiary C, q = quaternary C. High-resolution mass spectra (HRMS) were determined on a Finnigan MAT90 instrument. Elemental analysis was performed with Heraeus CHN-O-Rapid and Elementar vario MICRO CUBE instruments. Optical rotations were determined with a Perkin–Elmer 241 polarimeter (Na, 589 nm).

Crystal Structure Studies 11, 12, and 14: Single-crystal X-ray diffraction studies were carried out with a Bruker-Nonius APEXII diffractometer at 123(2) K using Mo-K_α radiation (λ = 0.71073 Å). The structures were solved by direct methods (SHELXS-97[30]), and refinement was carried out using SHELXL-97[30] (full-matrix least-squares refinement on F^2). The hydrogen atoms were localized by difference electron density determination and refined using a "riding" model. The absolute structure of **14** could not be determined reliably [refinement of Flack's x-parameter x = –0.7(12)[31]], and **11** is a redetermination of *N*,*N*-dimethyldiketopiperazine at 123 K.[32] Important data from the data collection, structure solution and refinement are listed in Table 1.

CCDC-687884 (for **11**), -687885 (for **12**) and -687886 (for **14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Microwave Irradiation Experiments: All microwave experiments were performed using the CEM Discover Synthesizer possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz.[33] Experiments were carried out in standard microwave process Pyrex vials (capacity 10 mL) using the high absorbance level. Reaction time reflects irradiation times at the set reaction temperature (fixed hold times).

General Procedure for the Dimerization of α-Amino Acids: The amino acid (1 mmol) was suspended in toluene (3 mL) with few drops of 1,3-dimethylimidazolium dimethylphosphate. Triethylamine (4 mmol) and methyl dichlorophosphite (1 mmol) were added via cannula. After irradiation under closed-vessel microwave conditions at 145 °C for 1 h, the solution was filtered, and the precipitate was washed with hot toluene. The filtrate was evaporated, and the resulting crude product was purified by flash column chromatography, if necessary.

(*S*,*S*)-Octahydrodipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (9a): 151 mg, 91% (scale 1.7 mmol). R_f = 0.27 (EE). $[\alpha]_D^{20}$ = 130.3 ($CHCl_3$, c = 1.00). M.p. 138–145 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.80–2.04 (m, 4 H, 2×CH_2), 2.06–2.20 (m, 2 H, CH_2), 2.22–2.34 (m, 2 H, CH_2), 3.45–3.53 (m, 4 H, 3-CH_2, 8-CH_2), 4.14 (t, J = 8.11 Hz, 2 H, 5a-H, 10a-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2 (s, 2 C, C-2, C-7), 27.6 (s, 2 C, C-1, C-6), 45.1 (s, 2 C, C-3, C-8), 60.4 (t, 2 C, C-5a, C-10a), 166.3 (q, 2 C, C-5, C-10) ppm. IR (neat): $\tilde{\nu}$ = 3851 (vw), 3310 (w), 3089 (w), 2974 (m), 2848 (m), 2775 (vw), 2369 (vw), 2224 (vw), 2119 (vw), 1985 (vw), 1938 (vw), 1802 (w), 1667 (m), 1670 (w), 1487 (w), 1434 (m), 1337 (m), 1318 (w), 1292 (m), 1237 (m), 1211 (m), 1164 (m), 1070 (w), 1052 (w), 1028 (w), 1003 (w), 970 (w), 919 (w), 881 (w), 844 (w), 795 (vw), 773 (w), 633 (w), 598 (w), 555 (w), 487 (w), 472 (w) cm^{-1}. EI–MS (70 eV): m/z (%) = 194 (97) [M^+], 138 (25), 110 (17), 96 (23), 70 (91), 55 (15), 41 (100). HRMS ($C_{10}H_{14}N_2O_2$): calcd. 194.1055; found 194.1059. $C_{10}H_{14}N_2O_2$ (194.1): calcd. C 61.84, H 7.27, N 14.42; found C 61.42, H 7.24; N 14.43.

(2*R*,4*S*,7*R*,9*S*)-2,7-Bis(*tert*-butyldimethylsilanyloxy)octahydrodipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (9b): 16 mg, 86% (scale 0.1 mmol). $[\alpha]_D^{20}$ = –58.3 (MeOH, c = 1.01). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 [s, 12 H, 2×(CH_3)$_2$], 0.87 (s, 18 H, *t*Bu), 2.05–2.13 (m, 2 H, 2×CH_2N), 2.25–2.32 (m, 2 H, 2×CH_2N), 3.49 (d, J = 12.6 Hz, 2 H, CH_2CH), 3.58–3.64 (m, 2 H, CH_2CH), 4.48 (t, J = 3.7 Hz, 2 H, CH_2CH), 4.53–4.58 (m, 2 H, C*H*OSi) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7 (p, 4 C, 4×*C*H$_3$), 18.1 (q, 2 C), 25.8 (p, 6 C, *t*Bu), 37.8 (s, 2 C, 2×CH*C*H$_2$), 54.6 (s, 2 C, 2×*C*H$_2$N), 59.2 (s, 2 C, 2×*C*HCH$_2$), 69.7 (t, 2 C, 2×*C*HOSi), 166.8 (q, 2 C, 2×*C*O) ppm. IR (neat): $\tilde{\nu}$ = 3321 (w), 2962 (m), 2859 (m), 1669 (m), 1435 (m), 1362 (w), 1305 (w), 1262 (m), 1221 (w), 1096 (m), 1020 (m), 921 (w), 881 (w), 803 (w), 700 (w), 622 (w) cm^{-1}. EI–MS (70 eV): m/z (%) = 397 (100), 369 (14) [M^+], 253 (4). HRMS ($C_{22}H_{41}N_2O_4Si_2$): calcd. 453.2605; found 453.2611.

(2*R*,4*S*,7*R*,9*S*)-2,7-Bis(benzyloxy)octahydrodipyrrolo[1,2-*a*:1′,2′-*d*]-pyrazine-5,10-dione (9c): 38 mg, 96% (scale 0.2 mmol). $[\alpha]_D^{20}$ = –4.02 (MeOH, c = 1.02). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.08–2.16 (m, 2 H, 2×CH_2), 2.57 (dd, J = 13.8 Hz, 2 H, 2×CH_2), 3.28–3.42 (m, 2 H, CH_2CH), 3.62 (dd, J = 13.4, 4.6 Hz, 2 H, 2×NCH_2), 3.68–3.80 (m, 2 H, 2×NCH_2), 4.15–4.32 (m, 2 H, 2×C*H*OBn), 4.54 (s, 4 H, 2×CH_2Ph), 7.23–7.39 (m, 10 H, Ar-H), ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.8 (s, 2 C, CH_2), 50.9 (s, 2 C, N*C*H$_2$), 58.8 (p, 2 C, 2×*C*H), 70.7 (p, 2 C, 2×*C*HBn), 75.4 (s, 2 C, 2×*C*H$_2$Ph), 127.5 (t, 4 C, Ar-C), 127.8 (t, 2 C, C-Ar), 128.4 (t, 4 C, C-Ar), 137.2 (q, 2 C, Ar-C), 166.2 (q, 2 C, *C*O) ppm. IR (neat): $\tilde{\nu}$ = 2942 (w), 2739 (w), 2678 (w), 2492 (m), 1669 (m), 1578 (w), 1454 (m), 1399 (w), 1362 (w), 1263 (m), 1201 (m), 1099 (m), 800 (w), 741 (w), 720 (w), 701 (w), 632 (w) cm^{-1}. EI–MS (70 eV): m/z (%) = 406 (7) [M^+], 315 (3), 300 (10), 90 (100). HRMS ($C_{24}H_{26}N_2O_4$): calcd. 406.1892; found 406.1896.

(2*R*,5a*S*,7*R*,10a*R*)-2,7-Di-*tert*-butoxyoctahydrodipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (9d): 86 mg, 97% (scale 0.5 mmol). R_f = 0.05 (hexane/EE, 3:1). $[\alpha]_D^{20}$ = –48.73 ($CHCl_3$, c = 0.87). M.p. 119–123 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 18 H, 6×CH_3), 2.12–2.26 (m, 4 H, 1-H, 6-H), 3.31–3.40 (m, 2 H, 3-H, 8-H), 3.62–3.72 (m, 2 H, 3-H, 8-H), 4.18–4.25 (m, 2 H, 5a-H, 10a-H), 4.38–4.47 (m, 2 H, 2-H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 (p, 6 C, 6×*C*H$_3$), 36.4 (s, 2 C, C-1, C-6), 53.4 (s, 2 C, C-3, C-8), 58.9 (t, 2 C, C-5a, C-10a), 68.1 [q, 2 C, 2×*C*(CH$_3$)$_3$], 74.3 (t, 2 C, C-2, C-7), 166.5 (q, 2 C, C-5, C-10) ppm. IR (neat): $\tilde{\nu}$ = 3314 (w), 2968 (s), 2870 (m), 1744 (m), 1657 (s), 1437 (s), 1390 (s), 1363 (s), 1313 (m), 1292 (m), 1263 (m), 1194 (s), 1147 (m), 1127 (m), 1096 (s), 1079 (s), 1045 (m), 1014 (s), 973 (w), 902 (m), 883 (m), 850 (w), 760 (w), 727 (w), 650 (w), 632 (w), 587 (w), 482 (w), 412 (w) cm^{-1}. EI–MS (70 eV): m/z (%) = 338 (21) [M^+], 282 (10), 226 (31), 140 (9), 86 (9), 58 (48), 43 (100). HRMS ($C_{18}H_{30}N_2O_4$): calcd. 338.2206; found. 338.2204.

Table 1. Crystallographic data, structure solution and refinement of **11**, **12**, **14**.

	11	**12**	**14**
Empirical formula	$C_6H_{10}N_2O_2$	$C_{10}H_6N_2O_2$	$C_{12}H_{18}N_2O_2$
Formula weight	142.16	186.17	222.28
Temperature [K]	123(2)	123(2)	123(2)
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/n$ (No. 14)	$P2_1/n$ (No. 14)	$C2$ (No. 5)
a [Å]	6.9079(5)	5.410(1)	11.410(2)
b [Å]	6.0733(5)	5.701(1)	6.413(1)
c [Å]	18.0337(5)	12.938(2)	7.911(1)
α [°]	90	90	90
β [°]	102.706(5)	100.34(1)	102.62(2)
γ [°]	90	90	90
V [Å^3]	328.79(4)	392.56(12)	564.88(15)
Z	2	2	2
$D_{calcd.}$ [g cm^{-3}]	1.436	1.575	1.307
Absorption coefficient [mm^{-1}]	0.109	0.114	0.090
$F(000)$	152	192	240
Crystal size [mm]	$0.25\times0.15\times0.10$	$0.50\times0.40\times0.30$	$0.45\times0.35\times0.25$
$2\theta_{max.}$ [°]	50	55	55
Limiting indices	$-7 \le h \le 8$ $-6 \le k \le 7$ $-7 \le l \le 9$	$-7 \le h \le 6$ $-7 \le k \le 7$ $-16 \le l \le 16$	$-14 \le h \le 14$ $-8 \le k \le 8$ $-10 \le l \le 10$
Reflections collected	1612	4766	5580
Unique reflections	574	891	1298
R_{int}	0.0346	0.0140	0.0544
Data/restraints/parameters	574/0/47	891/0/64	1298/1/73
GOF on F^2	1.089	1.123	1.078
R_1 [$I>2\sigma(I)$]	0.0366	0.0418	0.0348
wR_2 (all data)	0.0844	0.1144	0.0855
Largest diff. map peak/hole [e A^{-3}]	0.141/–0.230	0.393/–0.312	0.312/–0.201

1,4-Dimethylpiperazine-2,5-dione (11): 38 mg, 97% (scale 0.6 mmol). R_f = 0.42 (hexane/EE, 3:1). M.p. 136–139 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.90 (s, 6 H, 2 × CH_3), 3.91 (s, 4 H, 2 × CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.0 (p, 2 C, 2 × CH$_3$), 51.3 (s, 2 × CH$_2$), 162.8 (q, 2 C, C-2, C-5) ppm. IR (neat): $\tilde{\nu}$ = 3919 (vw), 3293 (w), 3153 (w), 2967 (m), 2936 (m), 2784 (w), 2676 (w), 2492 (w), 2421 (w), 2374 (w), 2275 (vw), 2056 (vw), 1971 (vw), 1739 (w), 1657 (m), 1555 (w), 1501 (m), 1446 (m), 1399 (m), 1340 (m), 1297 (w), 1254 (m), 1164 (m), 1135 (w), 1016 (m), 991 (w), 838 (w), 806 (w), 738 (m), 604 (m), 486 (vw), 411 (m) cm^{-1}. EI–MS (70 eV): *m*/*z* (%) = 142 (100) [M$^+$], 113 (9), 86 (9), 57 (31), 42 (24). HRMS ($C_6H_{10}N_2O_2$): calcd. 142.0742; found 142.0740.

Dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazine-5,10-dione (12): 70 mg, 84% (scale 0.9 mmol). R_f = 0.66 (hexane/EE, 3:1). M.p. 272–276 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.48 (t, J = 3.4 Hz, 2 H, 2-H, 7-H), 7.37 (dd, J = 3.4, 1.5 Hz, 2 H, 3-H, 8-H), 7.72 (dd, J = 3.4, 1.5 Hz, 2 H, 1-H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.7 (t, 2 C, C-2, C-7), 123.4 (t, 2 C, C-3, C-8), 123.7 (t, 2 C, C-1, C-6), 124.3 (q, 2 C, C-5a, C-10a), 150.9 (q, 2 C, C-5, C-10) ppm. IR (neat): $\tilde{\nu}$ = 3978 (w), 3390 (m), 3260 (w), 3127 (m), 3011 (w), 2954 (w), 2883 (w), 2850 (w), 2725 (w), 2604 (w), 2542 (w), 2476 (w), 2426 (w), 2359 (w), 2288 (w), 2252 (w), 2225 (w), 2141 (w), 2089 (w), 2036 (w), 1964 (w), 1937 (w), 1881 (w), 1816 (m), 1771 (m), 1701 (s), 1627 (m), 1558 (s), 1479 (m), 1458 (s), 1414 (s), 1324 (s), 1256 (m), 1221 (m), 1182 (m), 1149 (m), 1069 (s), 1022 (m), 997 (m), 910 (m), 857 (m), 778 (m), 738 (s), 704 (m), 618 (m), 588 (m), 439 (w) cm^{-1}. EI–MS (70 eV): *m*/*z* (%) = 186 (100) [M$^+$], 155 (15), 130 (16), 93 (33), 77 (10), 65 (11), 58 (11), 43 (23). HRMS ($C_{10}H_6N_2O_2$): calcd. 186.0429; found 186.0430.

Pyrazino[1,2-*a*;4,5-*a*′]diindole-6,13-dione (13): 78 mg, 90% (scale 0.6 mmol). R_f = 0.58 (hexane/EE, 1:1). M.p. 249–254 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (ddd, J = 1.0, 7.0, 8.5 Hz, 2 H, 4-H, 11-H), 7.15 (dd, J = 1.0, 8.5 Hz, 2 H, 3-H, 10-H), 7.25 (ddd, J = 1.0, 7.0, 8.5 Hz, 2 H, 2-H, 9-H), 7.43 (dd, J = 0.9, 8.2 Hz, 2 H, 7-H, 14-H), 7.63 (dd, J = 0.9, 8.2 Hz, 1-H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.3 (t, 2 C, C-7, C-14), 113.3 (t, 2 C, C-4, C-11), 121.4 (t, 2 C, C-3, C-10), 123.2 (t, 2 C, C-1, C-8), 126.0 (t, 2 C, C-2, C-9), 128.5 (q, 2 C, C-7a, C-14a), 128.7 (q, 2 C, C-6a, C-13a), 139.1 (q, 2 C, C-4a, C-11a), 164.0 (q, 2 C, C-6, C-13) ppm. IR (neat): $\tilde{\nu}$ = 3335 (m), 3122 (m), 3057 (m), 2953 (m), 2489 (w), 2035 (w), 1949 (w), 1917 (w), 1882 (w), 1696 (s), 1561 (m), 1530 (m), 1478 (m), 1449 (m), 1365 (m), 1344 (m), 1314 (m), 1259 (m), 1230 (m), 1199 (m), 1156 (m), 1120 (m), 1079 (m), 1008 (m), 992 (m), 938 (m), 880 (m), 853 (m), 825 (m), 772 (m), 747 (m), 701 (m), 662 (m), 607 (w), 579 (w), 565 (w), 539 (m), 478 (w), 435 (m) cm^{-1}. EI–MS (70 eV): *m*/*z* (%) = 286 (100) [M$^+$], 143 (33), 115 (38), 57 (11), 43 (19). HRMS ($C_{18}H_{10}N_2O_2$): calcd. 286.0742; found 286.0745.

(5a*S*,10a*S*)-5a,10a-Dimethyloctahydrodipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (14): 58 mg, 86% (scale 0.6 mmol). M.p. 178–180 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 6 H, 2 × CH_3), 1.80–2.13 (m, 8 H, 4 × CH_2), 3.44–3.51 (m, 2 H, 2 × NCH_2), 3.73–3.80 (m, 2 H, 2 × NCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (s, 2 C, C-2, C-7), 24.8 (p, 2 C, 2 × CH$_3$), 36.4 (s, 2 C, C-1, C-6), 44.4 (s, 2 C, C-3, C-8), 66.1 (q, 2 C, C-5a, C-10a), 168.9 (q, 2 C, 2 × CO) ppm. IR (neat): $\tilde{\nu}$ = 3274 (m), 2963 (m), 2605 (m), 2497 (m), 1960 (w), 1654 (m), 1504 (m), 1459 (m), 1429 (m), 1376 (m), 1364 (m), 1332 (m), 1312 (m), 1261 (m), 1209 (m), 1166 (m), 1093 (m), 1018 (m), 946 (m), 904 (m), 868 (m), 802 (m), 752 (m), 699 (w), 651 (m), 623 (w) cm^{-1}. EI–MS (70 eV): *m*/*z* (%) = 222 (73) [M$^+$], 207 (10), 194 (39), 151 (19), 84 (100), 83 (33), 43 (11). HRMS ($C_{12}H_{18}N_2O_2$): calcd. 222.1368; found 222.1371.

(*S*,*S*)-(6a,7,13a,14)-Tetrahydropyrazino[1,2-*a*:4,5-*a*′]diindol-6,13-dione (15): 162 mg, 93% (scale 1.2 mmol). R_f = 0.38 (hexane/EE, 3:1).

$[\alpha]_D^{20}$ = –2.21 ($CHCl_3$, c = 1.00). M.p. 263–268 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.46 (dd, J = 9.6, 16.8 Hz, 2 H, 7,14-H), 3.82 (dd, J = 9.6, 16.8 Hz, 2 H, 7,14-H), 4.99 (dd, J = 9.6, 16.8 Hz, 2 H, 6a,13a-H), 7.13 (dt, J = 1.0, 8.0 Hz, 2 H, 1,8-H), 7.29 (t, J = 8.0 Hz, 4 H, 3,4,10,11-H), 8.13 (d, J = 8.0 Hz, 2 H, 2,9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.0 (s, 2 C, C-7,14), 61.6 (t, 2 C, C-6a,13a), 115.7 (t, 2 C, C-4,11), 125.0 (t, 4 C, C-2,3,9,10), 127.9 (t, 2 C, C-1,8), 129.7 (t, 2 C, C-7a,14a), 140.5 (q, 2 C, C-4a,11a), 164.2 (q, 2 C, *C*O) ppm. IR (neat): $\tilde{\nu}$ = 3344 (vw), 3069 (w), 3050 (w), 2898 (w), 2863 (m), 1793 (vw), 1681 (m), 1603 (w), 1483 (m), 1462 (m), 1446 (w), 1410 (m), 1343 (w), 1315 (w), 1245 (w), 1213 (w), 1182 (w), 1156 (w), 1131 (w), 1086 (w), 1018 (w), 996 (w), 928 (w), 867 (w), 849 (w), 776 (w), 756 (m), 713 (w), 647 (w), 563 (w), 528 (w) cm^{-1}. EI–MS (70 eV): m/z = 290 [M$^+$]. HRMS ($C_{18}H_{14}N_2O_2$): calcd. 290.1055; found 290.1051. $C_{18}H_{14}N_2O_2$ (290.1): calcd. C 74.47, H 4.86, N 9.65; found C 74.45, H 5.08, N 9.65.

(4a*S*,6a*S*,7a*S*,11a*S*,13a*S*,14a*S*)-Hexadecahydropyrazino[1,2-*a*:4,5-*a*′]diindole-6,13-dione (16): 82 mg, 97% (scale 0.6 mmol). R_f = 0.50 (hexane/EE, 3:1). $[\alpha]_D^{20}$ = 12.60 (MeOH, c = 0.50). M.p. 204–208 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91–1.04 (m, 2 H, CH_2), 1.09–1.25 (m, 2 H, CH_2), 1.26–1.40 (m, 2 H, CH_2), 1.44–1.53 (m, 2 H, CH_2), 1.55–1.72 (m, 4 H, 2 × CH_2), 1.73–1.82 (m, 2 H, CH_2), 1.92–2.50 (m, 2 H, CH_2), 2.23–2.43 (m, 6 H, 2 × CH_2, 2 × CH), 3.92–4.00 (m, 2 H, 4a-H, 11a-H), 4.11 (t, 2 H, 6a-H, 13a-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (s, 2 C, C-3, C-10), 23.3 (s, 2 C, C-2, C-9), 25.9 (s, 2 C, C-1, C-8), 27.3 (s, 2 C, C-4, C-11), 28.5 (s, 2 C, C-7, C-14), 36.2 (t, 2 C, C-7a, C-14a), 55.9 (t, 2 C, C-6a, C-13a), 60.5 (t, 2 C, C-4a, C-11a), 167.4 (q, 2 C, C-6, C-13) ppm. IR (neat): $\tilde{\nu}$ = 3307 (w), 2979 (m), 2928 (m), 2858 (m), 2670 (vw), 1660 (m), 1466 (m), 1411 (m), 1370 (m), 1347 (m), 1295 (w), 1262 (w), 1192 (w), 1175 (w), 1159 (w), 1134 (w), 1114 (w), 1077 (w), 1062 (w), 1022 (w), 950 (w), 933 (w), 910 (vw), 891 (w), 878 (w), 855 (w), 823 (w), 789 (w), 766 (vw), 677 (w), 667 (w), 610 (w), 577 (w), 555 (w), 526 (vw), 498 (w), 463 (w), 448 (m), 421 (m), 413 (m) cm^{-1}. EI–MS (70 eV): m/z (%) = 302 (100) [M$^+$], 274 (8), 208 (13), 178 (20), 151 (4), 124 (53), 81 (8). HRMS ($C_{18}H_{26}N_2O_2$): calcd. 302.1994; found 302.1997. $C_{18}H_{26}N_2O_2$ (302.2): calcd. C 71.49, H 8.67, N 9.26; found C 71.81, H 8.42, N 9.05.

General Procedure for the Synthesis of Cross-coupled 2,5-Diketopiperazines: The first amino acid (1 mmol) was suspended in toluene (4 mL) plus a few drops of 1,3-dimethylimidazolium dimethylphosphate. Triethylamine (4 mmol), methyldichlorophosphite (1 mmol) and the second amino acid (1.2 mmol) were added subsequently. After irradiation under closed vessel microwave conditions at 145 °C for 1 h, the solution was filtered and the precipitate was washed with hot toluene. The filtrate was evaporated, and the resulting crude product was purified by flash column chromatography, if necessary.

(5a*S*,12a*S*)-1,2,3,5a,6,12a-Hexahydropyrrolo[1′,2′:4,5]pyrazino[1,2-*a*]-indole-5,12-dione (17): 172 mg, 83% (scale 0.9 mmol). R_f = 0.04 (hexane/EE, 3:1). $[\alpha]_D^{20}$ = –2.93 ($CHCl_3$, c = 13.3). M.p. 159–163 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.87–2.08 (m, 2 H, CH_2), 2.24–2.42 (m, 2 H, CH_2), 3.30 (dd, J = 10.5, 16.8 Hz, 1 H, NCH_2), 3.54–3.60 (m, 2 H, 6-H) 3.64 (dd, J = 10.5, 16.8 Hz, 1 H, NCH_2), 4.29 (t, J = 7.8 Hz, 1 H, 12a-H), 4.81 (t, J = 9.8 Hz, 1 H, 5a-H), 7.03–7.08 (m, 1 H, Ar-H), 7.17–7.23 (m, 2 H, Ar-H), 8.01–8.05 (m, 1 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 (s, C-2), 27.5 (s, C-1), 30.0 (s, C-6), 45.4 (s, C-3), 60.7 (t, C-5a), 61.2 (t, C-12a), 115.5 (t, C-10), 124.7 (t, C-8), 149.9 (t, C-9), 127.6 (t, C-7), 129.9 (q, C-6a), 140.5 (q, C-10a), 165.1 (q, C-5), 165.5 (q, C-12) ppm. IR (neat): $\tilde{\nu}$ = 3318 (w), 3114 (w), 3080 (w), 2987 (m), 2960 (m), 2874 (m), 2623 (w), 1968 (w), 1666 (s), 1600 (m), 1487 (m), 1454 (m), 1413 (m), 1344 (m), 1307 (m), 1289 (m), 1250 (m), 1210 (m), 1162 (m), 1132 (m), 1091 (w), 1033 (w), 1001 (m), 956 (w), 919 (m), 868 (w), 846 (w), 793 (w), 768 (m), 711 (w), 644 (m), 599 (w), 555 (w), 531 (w), 498 (w), 478 (vw), 430 (m) cm^{-1}. EI–MS (70 eV): m/z (%) = 242 (100) [M$^+$], 214 (25), 194 (38), 186 (11), 174 (17), 144 (16), 131 (35), 117 (75), 89 (17), 83 (11), 77 (14), 70 (51), 58 (18), 43 (80), 41 (11). HRMS ($C_{14}H_{14}N_2O_2$): calcd. 242.1054; found 242.1050.

(5a*S*,6a*S*,10a*S*,12a*S*)-Dodecahydropyrrolo[1′,2′:4,5]pyrazino[1,2-*a*]-indole-5,12-dione (18): 188 mg, 88% (scale 0.9 mmol). R_f = 0.16 (hexane/EE, 3:1). $[\alpha]_D^{20}$ = –1.00 ($CHCl_3$, c = 1.10). M.p. 68–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.98 (m, 1 H, CH_2), 1.0–1.05 (m, 1 H, CH_2), 1.19–1.33 (m, 1 H, CH_2), 1.36–1.47 (m, 1 H, CH_2), 1.47–1.65 (m, 4 H, CH_2), 1.66–1.76 (m, 1 H, CH_2), 1.89–1.99 (m, 2 H, CH_2), 2.25–2.37 (m, 6 H, CH_2), 3.37 (m, 1 H, 10a-H), 3.87 (dd, J_{trans} = 11.9, J_{cis} = 6.2 Hz, 1 H, 12a-H), 3.99–4.09 (m, 1 H, 5a-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (s, C-9), 23.3 (s, C-2), 25.6 (s, C-8), 27.2 (s, C-7), 28.2 (s, C-10), 28.4 (s, C-1), 35.8 (s, C-6), 35.9 (t, C-6a), 44.8 (s, C-3), 55.6 (t, C-5a), 60.2 (t, C-12a), 60.3 (t, C-10a), 166.4 (q, C-5), 166.9 (q, C-12) ppm. IR (neat): $\tilde{\nu}$ = 3309 (w), 2929 (m), 2858 (m), 1661 (s), 1413 (s), 1371 (m), 1347 (m), 1295 (m), 1262 (m), 1175 (m), 1134 (w), 1115 (w), 1077 (w), 1022 (w), 952 (w), 919 (w), 891 (w), 854 (w), 822 (w), 787 (w), 729 (w), 666 (w), 641 (w), 610 (w), 577 (w), 556 (w), 501 (vw), 464 (vw), 449 (w), 424 (w) cm^{-1}. EI–MS (70 eV): m/z (%) = 248 (100) [M$^+$], 220 (11), 194 (11), 178 (10), 154 (13), 124 (35), 96 (12), 70 (46). HRMS ($C_{14}H_{20}N_2O_2$): calcd. 248.1525; found 248.1522.

(4a*S*,6a*S*,13a*S*,14a*S*)-1,2,3,4,4a,6a,7,13a,14,14a-Decahydropyrazino[1,2-*a*:4,5-*a*′]diindole-6,13-dione (19): 145 mg, 81% (scale 0.6 mmol). R_f = 0.04 (hexane/EE, 3:1). $[\alpha]_D^{20}$ = 5.08 ($CHCl_3$, c = 1.23). M.p. 198–203 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86–1.04 (m, 1 H, CH_2), 1.05–1.19 (m, 1 H, CH_2), 1.20–1.35 (m, 1 H, CH_2), 1.38–1.82 (m, 4 H, CH_2), 1.90–2.11 (m, 1 H, CH_2), 2.15–2.44 (m, 3 H, CH_2), 3.24 (dd, J_{trans} = 16.9, J_{cis} = 10.7 Hz, 1 H, 7-H), 3.62 (dd, J_{trans} = 16.9, J_{cis} = 10.7 Hz, 1 H, 7-H), 3.85–3.94 (m, 1 H, 4a-H), 4.29 (t, J = 8.3 Hz, 1 H, 13a-H), 4.66–4.74 (m, 1 H, 6a-H), 6.98–7.05 (m, 1 H, Ar-H), 7.13–7.23 (m, 2 H, Ar-H), 7.97–8.03 (m, 1 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (s, C-3), 23.1 (s, C-2), 25.6 (s, C-1), 27.3 (s, C-4), 28.3 (s, C-7), 29.7 (s, C-14), 35.9 (t, C-14a), 55.7 (t, C-13a), 56.1 (t, C-6a), 60.7 (t, C-4a), 115.2 (t, C-11), 124.4 (t, C-10), 124.8 (t, C-9), 127.5 (t, C-8), 129.9 (q, C-7a), 140.4 (q, C-11a), 165.4 (q, C-6), 167.2 (q, C-13) ppm. IR (neat): $\tilde{\nu}$ = 3331 (w), 3116 (w), 3069 (w), 2924 (m), 2859 (m), 1674 (s), 1601 (m), 1483 (m), 1461 (m), 1410 (m), 1348 (w), 1307 (w), 1247 (m), 1196 (w), 1164 (w), 1133 (w), 1086 (w), 1065 (w), 1008 (w), 978 (w), 955 (w), 932 (w), 907 (w), 891 (w), 971 (w), 858 (w), 787 (w), 757 (m), 676 (w), 654 (w), 609 (w), 557 (w), 528 (w), 501 (w), 448 (w), 422 (w) cm^{-1}. (EI, 70 eV) m/z (%): 302 (100), 296 (27) [M$^+$], 274 (11), 208 (15), 178 (20), 124 (63), 117 (13), 81 (19). HRMS ($C_{18}H_{20}N_2O_2$): calcd. 296.1525; found 296.1522.

(*S*)-2-Methyl-2,3,10,10a-tetrahydropyrazino[1,2-*a*]indole-1,4-dione (20): 121 mg, 93% (scale 0.6 mmol). R_f = 0.48 (hexane/EE, 3:1). $[\alpha]_D^{20}$ = –6.44 ($CHCl_3$, c = 0.51). M.p. 248–252 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.07 (s, 3 H, CH_3), 3.44 (dd, J_{gem} = 16.8, J = 10.3 Hz, 1 H, 10-H), 3.79 (dd, J_{gem} = 16.8, J = 9.0 Hz, 1 H, 10-H), 3.88–3.98 (m, 1 H, 3-H), 4.30–4.41 (m, 1 H, 3-H), 4.97 (dd, J = 10.3, 9.0 Hz, 1 H, 10a-H), 7.07–7.14 (m, 1 H, Ar-H), 7.21–7.30 (m, 2 H, Ar-H), 8.02–8.12 (m, 1 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1 (p, *C*H$_3$), 33.8 (s, C-10), 54.2 (s, C-3), 61.6 (t, C-10a), 115.7 (t, C-6), 125.0 (t, C-8), 127.9 (t, C-7), 129.7 (t, C-9), 140.4 (q, C-9a), 140.7 (q, C-5a), 164.2 (q, C-4), 166.9 (q, C-1) ppm. IR (neat): $\tilde{\nu}$ = 3344 (w), 3051 (m), 2898 (m), 2863 (w),

1681 (s), 1603 (m), 1483 (s), 1462 (m), 1410 (m), 1343 (m), 1315 (m), 1246 (m), 1213 (m), 1183 (w), 1155 (w), 1132 (m), 1086 (m), 1058 (w), 1018 (m), 996 (m), 930 (w), 867 (w), 849 (w), 777 (m), 755 (m), 712 (w), 647 (w), 599 (w), 564 (w), 528 (m), 421 (m) cm^{-1}. EI–MS (70 eV): *m*/*z* (%) = 216 (100) [M^+], 199 (12), 142 (27), 131 (12), 117 (40), 90 (10). HRMS ($C_{12}H_{12}N_2O_2$): calcd. 216.0899; found 216.0896.

(5a*S*,9a*S*,10a*S*)-2-Methyldecahydropyrazino[1,2-*a*]indole-1,4-dione (21): 113 mg, 91% (scale 0.6 mmol). R_f = 0.14 (hexane/EE, 3:1). $[\alpha]_D^{20}$ = –0.82 ($CHCl_3$, *c* = 1.83). M.p. 129–133 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.74–1.04 (m, 1 H, C*H*$_2$), 1.04–1.38 (m, 2 H, C*H*$_2$), 1.40–1.52 (m, 1 H, C*H*$_2$), 1.52–1.70 (m, 2 H, C*H*$_2$), 1.70–1.82 (m, 1 H, C*H*$_2$), 1.92–2.14 (m, 1 H, C*H*$_2$), 2.14–2.46 (m, 3 H, 9a-H, 10-H), 2.95 (s, 3 H, C*H*$_3$), 3.65–3.69 (m, 1 H, 5a-H), 3.69–3.73 (m, 1 H, 10a-H), 3.87–4.03 (m, 1 H, 3-H), 4.04–4.15 (m, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (s, C-7), 23.3 (s, C-8), 25.7 (s, C-9), 27.2 (s, C-6), 33.5 (s, C-10), 35.6 (p, *C*H$_3$), 36.1 (t, C-9a), 55.8 (s, C-3), 59.1 (t, C-10a), 60.4 (t, C-5a), 163.7 (q, C-4), 168.3 (q, C-1) ppm. IR (neat): $\tilde{\nu}$ = 2930 (m), 2859 (m), 1663 (m), 1448 (m), 1411 (m), 1370 (w), 1347 (w), 1294 (w), 1263 (w), 1195 (w), 1175 (w), 1114 (w), 1042 (w), 951 (w), 892 (w), 854 (w), 822 (w), 788 (w), 677 (w), 642 (w), 611 (w), 577 (w), 555 (w), 449 (w), 424 (w) cm^{-1}. EI–MS (70 eV): *m*/*z* (%) = 222 (2) [M^+], 128 (1), 58 (32), 43 (100), 39 (3). HRMS ($C_{12}H_{18}N_2O_2$): calcd. 222.1368; found 222.1370.

(*S*)-2-Methylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (22): 155 mg, 89% (scale 1.0 mmol). R_f = 0.70 (hexane/EE, 3:1). $[\alpha]_D^{20}$ = –9.24 ($CHCl_3$, *c* = 0.72). M.p. 68–74 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.68–1.79 (m, 1 H, 7-H), 1.80–1.90 (m, 1 H, 7-H), 1.92–2.04 (m, 1 H, 8-H), 2.08–2.19 (m, 1 H, 8-H), 2.80 (s, 3 H, C*H*$_3$), 3.34 (dd, *J* = 8.6, 5.5 Hz, 2 H, 6-H), 3.81 (s, 2 H, 3-H), 4.02 (t, *J* = 8.1 Hz, 1 H, 8a-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9 (s, C-7), 27.2 (s, C-8), 32.7 (p, *C*H$_3$), 44.7 (s, C-6), 51.1 (s, C-3), 60.0 (t, C-8a), 162.7 (q, C-4), 165.9 (q, C-1) ppm. IR (neat): $\tilde{\nu}$ = 3917 (w), 3304 (m), 3152 (m), 2973 (m), 2884 (m), 2420 (w), 2372 (w), 1739 (w), 1668 (m), 1440 (m), 1338 (m), 1259 (m), 1163 (m), 1070 (m), 1015 (m), 969 (w), 919 (m), 880 (w), 839 (m), 739 (m), 631 (m), 601 (m), 505 (w), 487 (w), 476 (w), 412 (w) cm^{-1}. EI–MS (70 eV): *m*/*z* (%) = 168 (69) [M^+], 142 (100), 140 (13), 112 (16), 83 (16). HRMS ($C_8H_{12}N_2O_2$): calcd. 168.0899; found 168.0897.

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