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The synthesis of new diastereomers of (4*S*,8a*S*)- and (4*R*,8a*S*)-4-phenyl-perhydropyrrole[1,2-*a*]pyrazine-1,3-dione

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Abstract—The synthesis of new (4*S*,8a*S*)- and (4*R*,8a*S*)-4-phenyl-perhydropyrrole[1,2-*a*]pyrazine-1,3-diones in the cyclocondensation reaction of the respective derivatives of L-prolineamide is described. The effect of the amount of NaOEt, temperature, and reaction time on the proportions of diastereomers formed in the cyclocondensation reaction was examined. The structures of the diastereomers were confirmed by GC/MS, HRMS, HPLC, XRD, and ^{1}H and ^{13}C NMR investigations.

1. Introduction

Numerous derivatives of various heterocyclic systems possessing the imido group as a part of their structure exhibit biological activity. The imido functionality is a significant structural element of many new medicines from different pharmacological groups.[1–9]

The discovery of synthetic methods for heterocyclic systems, which contain the imido group in their structure, is important, particularly with respect to the well studied group of compounds that exhibit affinity to the 5-HT_{1A} receptor. Among the most important of these agents, which affect serotonin neurotransmission, are the long chain aryl piperazines (LCAPs), which exhibit high affinity to the 5-HT_{1A} receptor.[5–17]

Important representatives of the LCAPs group introduced to therapeutics are Buspirone and Tandospirone (Fig. 1). These medicines proved to be a milestone in the treatment of anxiety through the mechanism of the serotoninergic 5-HT_{1A} receptor.[2,5–8,18,19]

The imide group in Buspirone occurs in its non-pharmacophoric part, but plays a major role in stabilizing the ligand–receptor complex. It also affects the lipophilicity of the ligand molecule, which in turn has a significant effect on its selectivity over other receptors, such as the 5-HT_{2A} or α_1-adrenergic ones.[6,10,11,13,20]

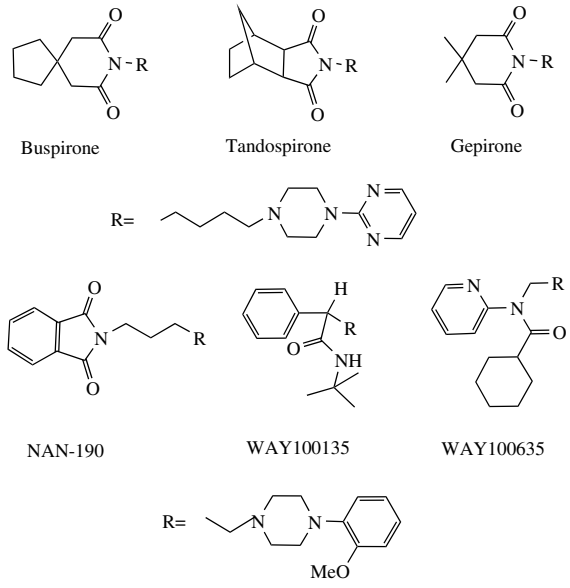

Figure 1. Biologically active LCAPs.

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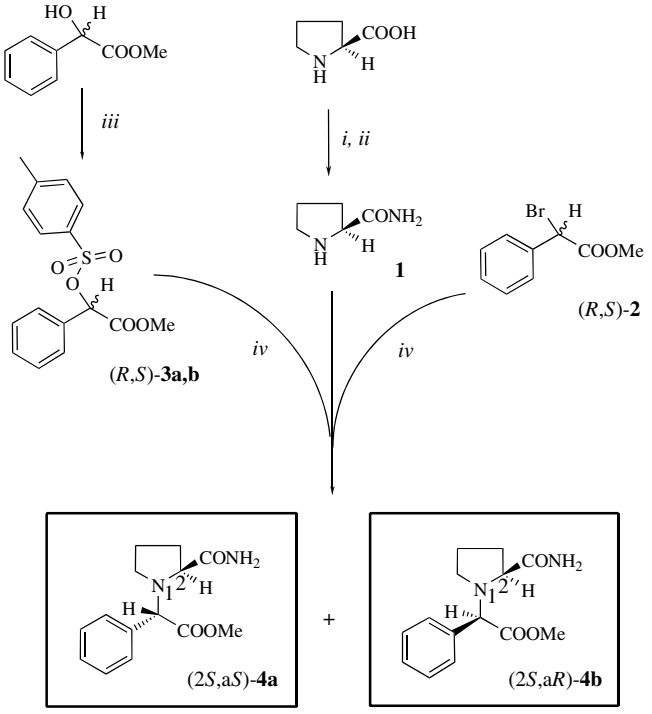


Scheme 1. Reagents and conditions: (i) $SOCl_2$, MeOH, reflux; (ii) $NH_{3(g)}$, MeOH, rt; (iii) TsCl, Et_3N, CH_2Cl_2, rt; (iv) K_2CO_3, CH_3CN, reflux.

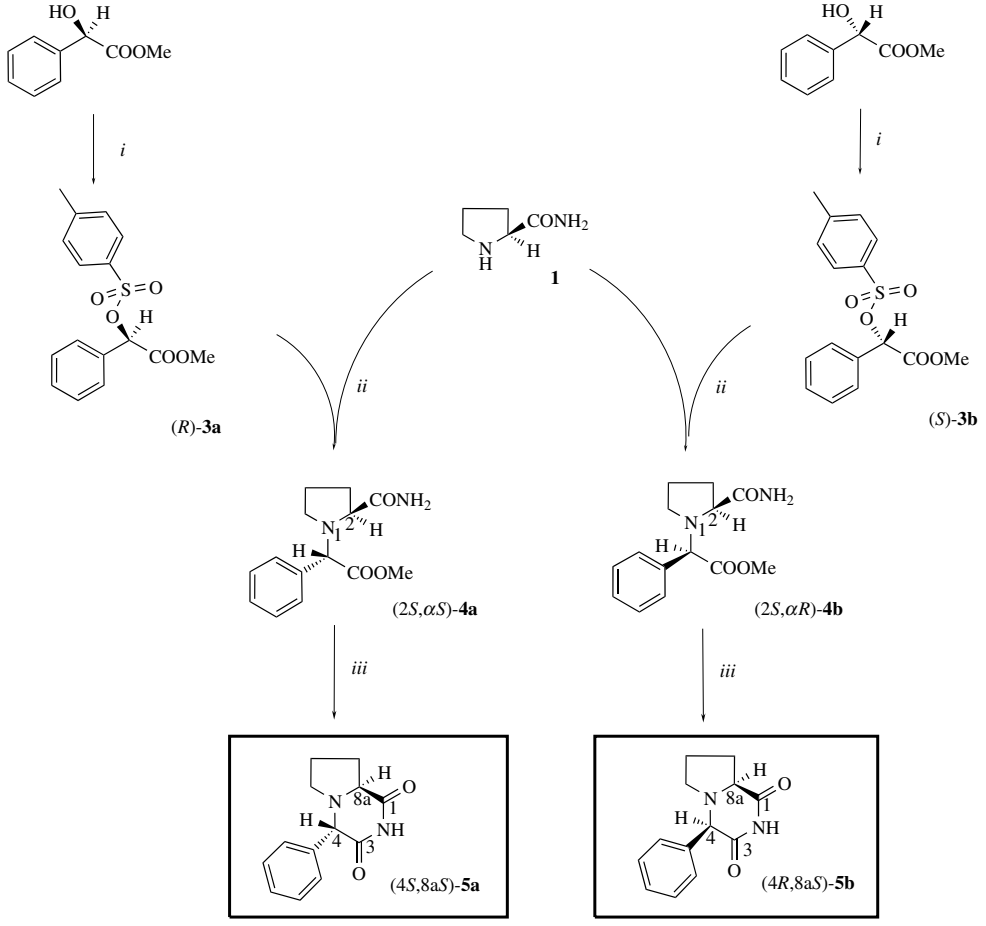
Herein we report the synthesis of a new pyrrole[1,2-*a*]pyrazine and the preparation of its two diastereomers **5a** and **5b**, which may serve as synthons for new pharmacologically active derivatives of the LCAPs group.

2. Results and discussion

2.1. Synthesis

The syntheses of title compounds (4*S*,8a*S*)-4-phenyl-perhydropyrrole[1,2-*a*]pyrazine-1,3-dione **5a** and (4*R*,8a*S*)-4-phenyl-perhydropyrrole[1,2-*a*]pyrazine-1,3-dione **5b** in the form of pure diastereomers were performed according to Schemes 1 and 2.

As the chiral substrate for the synthesis, (*S*)-prolineamide **1** was used, which was obtained by an esterification reaction and (*S*)-proline ammonolysis.[21,22] (*S*)-Prolineamide **1** was N-alkylated by reaction with (*R*,*S*)-α-bromo-phenylacetic methyl ester **2** or (*R*,*S*)-2-(4-toluenesulfonyloxy)-phenylacetic acid methyl ester **3a, b**, which afforded a mixture of two diastereomers (2*S*,α*S*)-α-(2-carbamoylpyrrolidinyl)-α-phenylacetic acid methyl ester (2*S*,α*S*)-**4a** and (2*S*,α*R*)-α-(2-carbamoylpyrrolidynyl)-α-phenylacetic acid methyl ester (2*S*,α*R*)-**4b** (Scheme 1). The content of the diastereomers in the post-reaction mixture was established



Scheme 2. Reagents and conditions: (i) TsCl, Et_3N, CH_2Cl_2, 0 °C; (ii) K_2CO_3, CH_3CN, reflux; (iii) EtONa, EtOH, rt.

by the GC/MS method (see Table 1). Crystallization of the mixture of diastereomers **4a/4b** from the hexane/ethyl acetate mixture (2:1 v/v) resulted in an analytically pure isomer **4a**, the structure of which was confirmed by GC/MS, ^{1}H NMR, and XRD. However, attempts to obtain pure diastereomer **4b** from the same mixture were unsuccessful.

Table 1. N-Alkylation of L-prolineamide with α-phenylacetic acid methyl ester derivatives

Entry[a]	Substrate	K_2CO_3 (equiv)	Yield[b] (%)	dr of **4a/4b**[c]
1	**2**	1	49	58:42
2	**2**	1/2	62	59:41
3	*rac*-**3**	1/2	56	55:45
4	**3a**	1/2	58	93:7
5	**3b**	1/2	67	12:88

[a] For all entries the reaction was performed by heating the mixture in CH_3CN for 5 h.
[b] Isolated yield.
[c] Estimated by means of GC/MS.

In both reactions, diastereomer **4a** was obtained in ~10–15% excess when compared to **4b**, most probably as a result of the stereoinductive effect of the stereogenic center of L-proline. These results agree with the data of Hwang et al., who also observed that diastereomer **4a** formed more rapidly and with higher yield than isomer **4b** in this reaction.[23] These authors did not provide any physicochemical data for the compounds obtained, except for elemental analysis.

Next, an alternative route for the N-alkylation reaction of (*S*)-prolinamide **1** was performed using either the chiral synthons of (*R*)-2-(4-toluenesulfonyloxy)-phenylacetic acid methyl ester **3a** or (*S*)-2-(4-toluenesulfonyloxy)-phenylacetic acid methyl ester **3b** (Scheme 2). The aim of this procedure was primarily to obtain pure diastereomer (2*S*,α*R*)-**4b**, which was impossible to isolate from the post-reaction mixture of diastereomers **4a/4b**.

The pure enantiomeric synthons that were needed for the next stage of investigations, such as **3a** and **3b**, were obtained according to the procedure given by Curotto et al. for compound **3b**; compound **3a** has not been described in the literature.[24,25] The purity of the enantiomers obtained was er 99:1 (HPLC). The obtained enantiomers (*R*)-**3a** and (*S*)-**3b** were subsequently subjected to reaction with **1**. Using **3a** for the reaction, a mixture of diastereomers was obtained with a very high excess of isomer (2*S*,α*S*)-α-(2-carbamoylpyrrolidinyl)-α-phenylacetic acid methyl ester **4a** in comparison with (2*S*,α*R*)-α-(2-carbamoylpyrrolidinyl)-α-phenylacetic acid methyl ester **4b** (93.3–6.7 GC/MS).

Next, using **3b** for the N-alkylation reaction, diastereoisomer **4b** was obtained, with a high excess in relation to isomer **4a**; the ratio of **4a** to **4b** was 11.6:88.4 (GC/MS) (see Table 1).

Compounds **4a** and **4b** were isolated as pure diastereomers by crystallization from a hexane/ethyl acetate system (3:1, v/v). The final compounds **5a** and **5b** were obtained by intramolecular cyclocondensation of the particular diastereomers **4a** and **4b**, respectively, relative to sodium ethoxylate. By cyclocondensation of diastereomer **4a**, (4*S*,8a*S*)-4-phenyl-perhydropyrrole[1,2-*a*]pyrazine-1,3-dione **5a** was obtained with a very high excess of **5a** isomer. Cyclization of compound **4b** afforded diastereomer (4*R*,8a*S*)-4-phenyl-perhydropyrrole[1,2-*a*]pyrazine-1,3-dione **5b**, but in a much lower proportion (71.7:28.3) (see Table 2 and Scheme 2).

Table 2. Intramolecular cyclocondensation of **4a** and **4b** in basic medium

Entry	Substrate	EtONa (equiv)	Temperature (°C)	Time	Yield[a] (%)	dr of **5a/5b**[b]
1	**4a**	2	rt	10 min	82	87:13
2	**4a**	1.1	rt	10 min	96	95:5
3	**4a**	1.1	−10 to −5	3.5 h	91	94:6
4	**4b**	2	rt	10 min	73	32:68
5	**4b**	1.1	rt	10 min	89	28:72
6	**4b**	1.1	−10 to −5	3.5 h	80	30:70

[a] Isolated yield.
[b] Estimated by means of HPLC.

In the cyclocondensation reaction, the ratio between the obtained diastereomers **5a/5b** was largely affected by the amount of EtONa, as well as by the temperature and reaction time. An excess of two equivalents of ethoxylate resulted in partial epimerization of substrate **4b** (see Table 2).

Analytically pure diastereomers **5a** and **5b** were obtained by crystallization of the reaction product from either a MeOH/H_2O mixture (1:1, v/v) or hexane/ethyl acetate mixture (2:1, v/v).

2.2. NMR spectroscopy and XRD investigation

2.2.1. NMR spectroscopy. The structures for the specific diastereomers **4a** and **4b**, as well as **5a** and **5b**, were confirmed by analysis of the chemical shifts. For diastereomers (*S*,*S*)-**4a** and (*S*,*R*)-**4b**, the steric arrangement of proton H–C2 in relation to the remaining protons of the pyrrolidine ring was similar in both molecules and can be assumed to be pseudoaxial, as determined by the coupling constants and the shapes of multiplets of proton H–C2 and proton H–C8a, respectively. However, for diastereomers (*S*,*S*)-**5a** and (*S*,*R*)-**5b**, the configurations of the protons of the pyrrolidine ring differ. This difference reflects the rigidity of the molecular structure due to the coupling of the pyrrolidine ring with the pyrazine ring in the bicyclic system. Furthermore, a different configuration of the proton of the pyrrolidine ring is observed in both diastereomers. In the isomer (*S*,*R*)-**5b**, the H–C8a bond is probably situated outside of this section of the H–C8–H′ plane (see Newman projection, Fig. 2), which corresponds to the same coupling constants: $^3J = 8.3$ and the angles ~30° and ~140° (estimated according to the Karplus curve). In the case of isomer (*S*,*S*)-**5a**, this bond is probably situated inside the above-mentioned section of the plane, which corresponds to the coupling constants $^3J = 8.5$ and $^3J = 3.2$ and the angles ~30° and ~80° (Fig. 2).[26,27] This interpretation is also confirmed by the ^{13}C NMR spectra, which indicate considerable differences between the chemical shifts of the C8a carbons

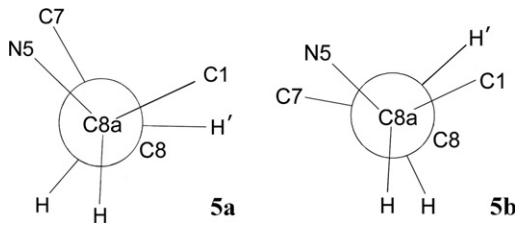


Figure 2. Newman projection of a C8a–C8 fragment of the molecules **5a** and **5b**.

(for **5a**: 57.3 ppm and for **5b**: 65.1 ppm); differences are also observed in the signals of carbons C6, C7, and C8.

Since the absolute configuration of **5b** proceeds from the structure obtained by X-ray analysis (see Section 2.2.2 XRD investigations), the relative stereochemistry of **5a** was ascertained by NOE ^{1}H NMR experiment. Contrary to **5b**, in the structure corresponding to configuration **5a** (4*S*,8a*S*) the interatomic distance between protons H-4 and H-8a should exclude any considerable NOE effect. In fact, in **5b** the irradiation of the H-8a resonance at 3.19 ppm resulted in a remarkable enhancement of the H-4 signal at 4.05 ppm, whereas in **5a** the analogous experiment with H-8a at 3.68 and H-4 at 4.87 ppm gave only a trace increase in intensity. The corresponding enhancement values for **5b** and **5a** were 6.5 and 0.36 (in %), respectively. The reverse order of irradiation, consisting in saturation of H-4 and analysis of the changes in the H-8a resonance, led to similar results and gave 6.9% and 0.35% enhancement, respectively, for **5b** and **5a**.

2.2.2. XRD investigation. The structure and stereochemistry of **4a** and **5b** were fully elucidated from a single crystal X-ray study.

The X-ray crystallographic analysis of **4a** showed two molecules, **A** and **B**, in the asymmetric unit cell with a

Table 3. Hydrogen-bonding geometry (Å and deg.) for **4a** and **5b**

D–H···A	*d*(D–H)	*d*(H···A)	*d*(D···A)	<(DHA)
Compound **4a**				
N9A–H9AB···O11B	0.86	2.58	3.004(2)	112
N9B–H9BB···O11A	0.86	2.60	3.037(3)	113
C2′A–H2′A···O11B	0.93	2.48	3.387(3)	164
C2′B–H2′B···O11A	0.93	2.70	3.606(3)	165
N9A–H9AA···O8B^{i}	0.86	2.08	2.935(2)	179
C13B–H13E···O8B^{i}	0.96	2.49	3.419(3)	163
N9B–H9BA···O8A^{ii}	0.86	2.11	2.969(2)	178
C13A–H13B···O8A^{ii}	0.96	2.45	3.395(3)	167
C4′B–H4′B···O8B^{iii}	0.93	2.45	3.368(3)	170
Symmetry codes: (i) $x-1,y,z$; (ii) $x+1,y,z$; (iii) $-x+1,y-0.5,-z+0.5$.				
Compound **5b**				
N2–H2A···O3^{i}	0.86	2.01	2.856(3)	168
C8–H8B···O1^{ii}	0.97	2.60	3.399(4)	140
Symmetry codes: (i) $-x+1,y-0.5,-z+2$; (ii) $-x,y+0.5,-z+1$.				

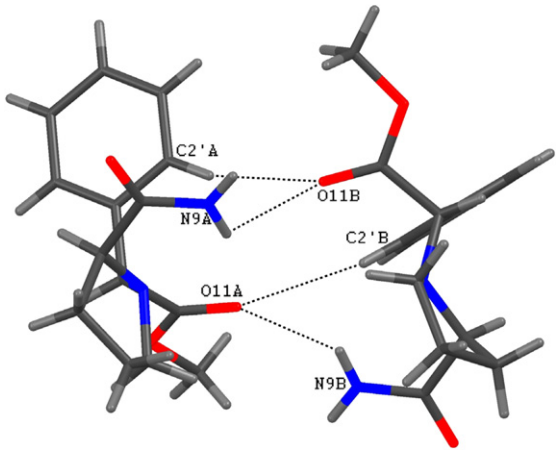


Figure 4. Molecules **A** and **B** of **4a** connected via intramolecular interactions.

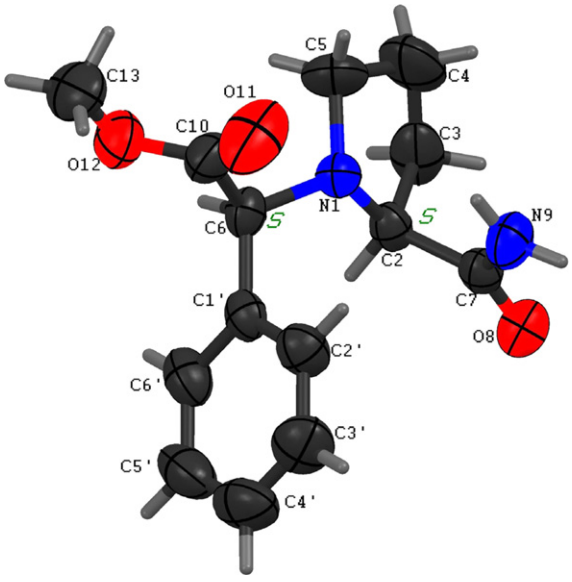


Figure 3. X-ray diffraction structure of molecule **A** of **4a**.

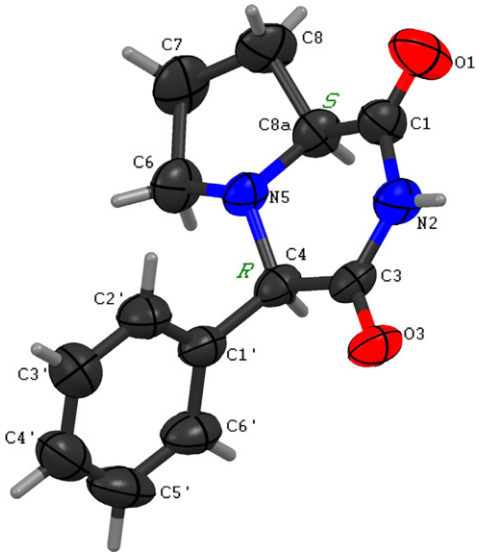


Figure 5. X-ray diffraction structure of **5b**.

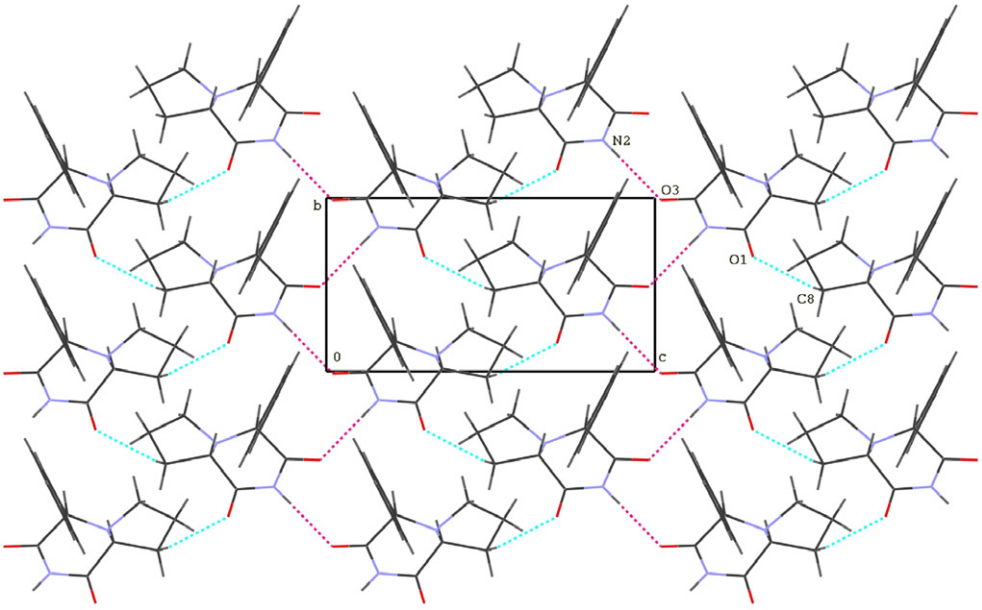


Figure 6. The packing arrangement of **5b** along the *a*-axis.

(*S*,*S*)-absolute configuration in both molecules (Fig. 3). This configuration was confirmed by the Flack parameter, which was refined to a value of −1.2(10).[28]

The solid state conformation of **4a** is stabilized by intra- and intermolecular hydrogen bonds (Table 3). The molecules **A** and **B** from the asymmetric unit are connected by N9···O11 and weak C2′···O11 interactions (Fig. 4). The other intermolecular contacts join the molecules, forming a three-dimensional network of interactions.

The X-ray diffraction analysis revealed that compound **5b** has an (*S*,*R*)-absolute configuration, as depicted in Figure 5. It was confirmed by the Flack parameter, which was refined to a value of −0.3(5).[28] The crystal structure of **5b** is stabilized by the intermolecular N···O and C···O interactions (see Table 3 and Fig. 6).

3. Conclusions

N-Alkylation of L-prolineamide **1** using (*R*)-2-(4-toluenesulfonyloxy)-phenylacetic acid methyl ester **3a** or (*S*)-2-(4-toluenesulfonyloxy)-phenylacetic acid methyl ester **3b** afforded pure diastereomers (2*S*,α*S*)-α-(2-carbamoylpyrrolidinyl)-α-phenylacetic acid methyl ester **4a** and (2*S*,α*R*)-α-(2-carbamoylpyrrolidine)-α-phenylacetic acid methyl ester **4b**. In an analogous reaction that used (*R*,*S*)-α-bromomethyl phenyl acetates **2a** and **2b** for N-alkylation, a mixture of diastereomers was obtained with the compound **4a** in excess in comparison with **4b**, a result of stereoinduction by the stereogenic center of L-prolineamide **1** in this reaction.

In the reaction of the intramolecular cyclization to EtONa of diastereomers **4a** or **4b**, appropriate mixtures of diastereomers **5a**/**5b** were obtained with a very high excess of compound **5a** as compared with **5b**. Even in the case where the cyclocondensation was initiated with **4b**, a much smaller yield of **5b** was obtained.

In the case of the N-alkylation of L-prolineamide **1**, a high yield of diastereomer (*S*,*S*)-**4a** was observed, and its subsequent cyclization to compound (*S*,*S*)-**5a** proceeded with a very high excess of **5a** in comparison with isomer **5b**. In the case of diastereomer (*S*,*R*)-**4b**, both its yield and cyclization proceeded to lesser extent than the comparable compounds **4a** and **5a**.

In the cyclization reaction, the proportions between the obtained diastereomers **5a**/**5b** were affected by the amount of EtONa used as well as by the time and temperature of the reaction.

4. Experimental

4.1. General methods

Melting points were determined on an Electrothermal 9100 apparatus with open capillary tubes and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AVANCE 400WB instrument. In some cases, ^{1}H NMR spectra were recorded on a Varian UNITY plus-500 spectrometer. The NOE ^{1}H NMR experiment was performed on a Bruker DRX 500 Avance instrument at 30 °C in $CDCl_3$. Chemical shifts (δ) are expressed in parts per million relative to tetramethylsilane used as the internal reference. Coupling constants (J) are in Hertz (Hz). GC/LRMS analyses were performed on a Hewlett Packard HP 5890 apparatus with an MSD 5972 spectrometer. HRMS (ESI) analyses were recorded on a Mariner (PE Biosystems) instrument. Specific rotations were measured with a Perkin–Elmer 341 Polarimeter at 20 °C. Thin-layer chromatography was run on Merck Silica Gel 60 F_{254}

plates. The compounds were visualized by UV light (254 nm) or iodine. Flash column chromatography was carried out on Merck Silica Gel 60 (230–400 mesh ASTM). Chiral HPLC was performed on Chiralpak IA 46 × 250 mm (Daicel Chemical Industries Ltd) column with 225 nm detector. L-Proline, (*S*,*R*)-, (*S*)-(+)-, and (*R*)-(−)-methyl mandelate were high-grade commercial products purchased from Lancaster and used without further purification. Other reagents and solvents were purified by standard procedures.

4.2. L-Prolineamide 1

To a stirred, cooled (−20 °C) solution of L-proline (50 g, 0.434 mol) in anhydrous methanol (200 mL, 4.938 mol) thionyl chloride (32.8 mL, 0.450 mol) was added dropwise, keeping the temperature at −5 to +5 °C. The mixture was then allowed to reach room temperature and then heated at reflux until sulfur dioxide ceased to evolve (2 h). The solution was then concentrated under reduced pressure. The resulting pale yellow oil was allowed to stand in a vacuum dessicator over potassium hydroxide overnight. The crude oil was suspended in ethyl acetate (200 mL) and triethylamine (69.0 mL, 0.495 mol) was added in one portion. The resulting solid was filtered off and washed with ethyl acetate. The combined filtrates were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was distilled under reduced pressure. The fraction collected at 95–97 °C (34 mm Hg) was dissolved in methanol (150 mL). The solution was saturated with gaseous ammonia at −20 °C and allowed to stand at room temperature for 4 days. The mixture was concentrated under reduced pressure. The resulting solid was recrystallized from ethyl acetate to yield 35.7 g (72%) of title compound **1**. White solid, mp 98–101 °C; $[\alpha]_D = -92.8$ (*c* 2, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.74 (m, 2H, C4H$_2$), 1.93 (m, 1H, C3H″), 2.15 (m, 1H, C3H′), 2.47 (s, 1H, N1H), 2.95 (m, 1H, C5H″), 3.01 (m, 1H, C5H′), 3.44 (m, 1H, C2H), 6.27 (br s, 1H, NH″), 7.44 (br s, 1H, NH′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.4 (C4), 30.8 (C3), 40.4 (C5), 60.6 (C2), 170.0 (CO).

4.3. Preparation of (*R*)-(−)- and (*S*)-(+)-2-(4-toluenesulfonyloxy)-phenylacetic acid methyl esters 3a and 3b

To a stirred, cooled (−15 °C) solution of 4-toluenesulfonyl chloride (11.44 g, 60 mmol) in dry dichloromethane (100 mL), (*R*)-(−)-, or (*S*)-(+)-methyl mandelate (2.49 g, 15 mmol) and triethylamine (2.09 mL, 15 mmol) were added in one portion. The solution was stirred at −5 to +5 °C for 7.5 h. The mixture was then washed with diluted hydrochloric acid (100 mL) and brine (100 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate 5:1, then 3:1, v/v) to yield the title compound.

4.3.1. (*R*)-(−)-2-(4-Toluenesulfonyloxy)-phenylacetic acid methyl ester 3a. Yield: 61%; white wax; mp 58–59 °C; $[\alpha]_D = -63.3$ (*c* 2, $CHCl_3$); IR (KBr): 1177, 1366, 1759; TLC (hexane/ethyl acetate 2:1): $R_f = 0.57$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 5.79 (s, 1H, CH), 7.25–7.38 (m, 7H, C2′H, C3′H, C4′H, C5′H, C6′H, C3″H, C5″H), 7.76 (d, $^3J = 8.0$, 2H, C2″H, C6″H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.8 (CH_3), 53.1 (OCH_3), 79.0 (CH), 127.7 (C2′, C6′), 128.3 (C2″, C6″), 129.0 (C3′, C5′), 129.8 (C4′), 129.9 (C3″, C5″), 133.0 (C1″), 133.6 (C1′), 145.3 (C4″), 168.0 (C=O); HRMS (ESI): $(M+Na)^+$ calcd for $C_{16}H_{16}O_5NaS$, 343.0611; found, 343.0618; HPLC: er = 99:1 (Chiralpak IA 46 × 250 mm column with a 225 nm detector, mobile phase: hexane/ethanol 95:5, flow rate: 0.8 mL/min, sample: 5 μL, sample concentration: 0.1 mg/mL temperature: 25 °C, retention time: 20.0 min).

4.3.2. (*S*)-(+)-2-(4-Toluenesulfonyloxy)-phenylacetic acid methyl ester 3b. Yield: 52%; white wax; mp 56–58 °C; $[\alpha]_D = +61.4$ (*c* 2, $CHCl_3$) {lit.[25] mp 57–58 °C; $[\alpha]_D = +61.7$ (*c* 1.085, $CHCl_3$)}; IR (KBr): 1175, 1364, 1760; TLC (hexane/ethyl acetate 2:1): $R_f = 0.57$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 3H, CH_3) 3.67 (s, 3H, OCH_3), 5.79 (s, 1H, CH), 7.25–7.38 (m, 7H, C2′H, C3′H, C4′H, C5′H, C6′H, C3″H, C5″H), 7.76 (d, $^3J = 8.0$, 2H, C2″H, C6″H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.8 (CH_3), 53.1 (OCH_3), 79.0 (CH), 127.7 (C2′, C6′), 128.3 (C2″, C6″), 129.0 (C3′, C5′), 129.8 (C4′), 129.9 (C3″, C5″), 133.0 (C1″), 133.6 (C1′), 145.3 (C4″), 168.0 (C=O); HRMS (ESI): $(M+Na)^+$ calcd for $C_{16}H_{16}O_5NaS$, 343.0611; found, 343.0626; HPLC: er = 99:1 (Chiralpak IA 46 × 250 mm column with 225 nm detector, mobile phase: hexane/ethanol 95:5, flow rate: 0.8 mL/min, sample: 5 μL, sample concentration: 0.1 mg/mL temperature: 25 °C, retention time: 21.7 min).

4.3.3. (2*S*,α*S*)-α-(2-Carbamoylpyrrolidinyl)-α-phenylacetic acid methyl ester 4a. A solution of **3a** (1.41 g, 4.4 mmol), **1** (0.51 g, 4.4 mmol), and potassium carbonate (0.30 g, 2.2 mmol) in acetonitrile (25 mL) was stirred at reflux until TLC showed no further reaction (5 h). The mixture was cooled, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 2:1, v/v, then ethyl acetate) to yield 0.66 g (58%) of **4a** and **4b** (dr = 93:7). Recrystallization from hexane/ethyl acetate (2:1, v/v) afforded pure **4a** diastereomer. White crystals; mp 124–125 °C; $[\alpha]_D = +29.7$ (*c* 2, MeOH); IR (KBr): 1161, 1200, 1682, 1751, 3175, 3410; TLC (toluene/ethanol 6:1): $R_f = 0.28$; ^{1}H NMR (500 MHz, MeOD): δ 1.77 (m, 1H, H′-4), 1.80–1.90 (m, 2H, H′-3, H-4), 2.14 (m, 1H, H-3), 2.80 (m, 1H, $^2J = 9.5$, $^3J = 9.5$, $^3J = 5.7$, H′-5), 3.10 (m, 1H, $^2J = 9.3$, $^3J = 7.2$, $^3J = 2.9$, H-5), 3.31 (dd, 1H, $^3J = 10.3$, $^3J = 2.9$, H-2), 3.68 (s, 3H, CH_3), 4.52 (s, 1H, H-α), 7.31–7.36 (m, 3H, H-3′, H-4′, H-5′), 7.37–7.43 (m, 2H, H-2′, H-6′). ^{13}C NMR (100 MHz, MeOD): δ 25.5 (C-4), 32.3 (C-3), 52.7 (CH_3), 53.2 (C-5), 65.6 (C-2), 71.5 (C-α), 129.7 (C-4′), 129.8 (C-3′, C-5′), 130.3 (C-2′, C-6′), 137.9 (C-1′), 174.4 (C-7), 181.3 (C-6); GC/MS (LR): $m/z = 218$ $(M-CONH_2)^+$, retention time: 34.13 min; HRMS (ESI): $(M+Na)^+$ calcd for $C_{14}H_{18}N_2O_3Na$, 285.1210; found, 285.1215.

4.3.4. (2*S*,α*R*)-α-(2-Carbamoylpyrrolidinyl)-α-phenylacetic acid methyl ester 4b. A solution of **3b** (1.35 g, 4.2 mmol), **1** (0.48 g, 4.2 mmol), and potassium carbonate (0.29 g, 2.1 mmol) in acetonitrile (25 mL) was stirred under reflux

until TLC showed no further reaction (5 h). The mixture was cooled, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 2:1, v/v, then ethyl acetate) to yield 0.74 g (67%) of **4a** and **4b** (dr = 12:88). Recrystallization from heptane/ethyl acetate (3:1, v/v) afforded pure **4b** diastereomer. White crystals; mp 89–90 °C; $[\alpha]_D = -116.4$ (*c* 2, MeOH); IR (KBr): 1161, 1204, 1627, 1728, 3186, 3406; TLC (toluene/ethanol 6:1): $R_f = 0.28$; ^{1}H NMR (500 MHz, MeOD): δ 1.72–1.80 (m, 2H, H-4, H′-4), 1.87 (m, 1H, H′-3), 2.20 (m, 1H, H-3), 2.57 (m, 1H, $^2J = 9.8$, $^3J = 9.8$, $^3J = 6.3$, H′-5), 3.06 (m, 1H, $^2J = 9.5$, $^3J = 6.6$, $^3J = 2.4$, H-5), 3.57 (dd, 1H, $^3J = 10.2$, $^3J = 2.4$, H-2), 3.65 (s, 3H, CH_3), 4.61 (s, 1H, H-α), 7.30–7.36 (m, 3H, H-3′, H-4′, H-5′), 7.37–7.44 (m, 2H, H-2′, H-6′). ^{13}C NMR (100 MHz, MeOD): δ 25.4 (C-4), 32.5 (C-3), 52.5 (CH_3), 53.9 (C-5), 65.1 (C-2), 71.4 (C-α), 129.6 (C-4′), 129.8 (C-3′, C-5′), 131.3 (C-2′, C-6′), 137.9 (C-1′), 173.9 (C-7), 181.8 (C-6); GC/MS (LR):m/z = 218 $(M-CONH_2)^+$, retention time: 33.71 min; HRMS (ESI): $(M+Na)^+$ calcd for $C_{14}H_{18}N_2O_3Na$, 285.1210; found, 285.1220.

4.3.5. (4*S*,8a*S*)-4-Phenyl-perhydropyrrole[1,2-*a*]pyrazine-1,3-dione 5a. To a stirred solution of sodium ethoxylate (50 mg, 2.1 mmol of sodium) in absolute ethanol (25 mL), **4a** (0.50 g, 1.9 mmol) was added in one portion. The solution was then stirred at room temperature for 10 min. The mixture was poured on ice/water (150 mL), acidified with a 5% solution of sulfuric acid, and extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield 0.42 g (96%) of a mixture of **5a** and **5b** (dr = 95:5). Recrystallization from methanol/water (1:1, v/v) afforded pure **5a** diastereomer. White needles; mp 125–126 °C; $[\alpha]_D = -138.15$ (*c* 2, $CHCl_3$); IR (KBr): 1669, 1703; TLC (toluene/ethanol 6:1): $R_f = 0.44$; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.84–1.99 (m, 2H, H-7, H′7), 2.25 (m, 1H, H′-8), 2.30 (m, 1H, H-8), 2.81 (pq, 1H, $^2J = 8.8$, $^3J = 8.8$, H′-6), 3.20 (m, 1H, $^2J = 8.8$, $^3J = 8.8$, $^3J = 3.9$, H-6), 3.68 (dd, 1H, $^3J = 8.5$, $^3J = 3.2$, H-8a), 4.87 (s, 1H, H-4), 7.31–7.36 (m, 1H, H-4′), 7.36–7.41 (m, 2H, H-3′, H-5′), 7.41–7.46 (m, 2H, H-2′, H-6′), 8.30 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6 (C-7), 27.5 (C-8), 51.9 (C-6), 57.3 (C-8a), 64.2 (C-4), 127.3 (C-3′, C-5′), 128.6 (C-4′), 129.1 (C-2′, C-6′), 134.2 (C-1′), 172.0 (C-3), 174.2 (C-1); HRMS (ESI): $(M+H)^+$ calcd for $C_{13}H_{15}N_2O_2$, 231.1128; found, 231.1124.

4.3.6. (4*R*,8a*S*)-4-Phenyl-perhydropyrrole[1,2-*a*]pyrazine-1,3-dione 5b. To a stirred solution of sodium ethoxylate (50 mg, 2.1 mmol of sodium) in absolute ethanol (25 mL), **4b** (0.50 g, 1.9 mmol) was added in one portion. The solution was then stirred at room temperature for 10 min. The mixture was poured onto ice/water (150 mL), acidified with a 5% solution of sulfuric acid, and extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield 0.39 g (89%) of **5a** and **5b** (dr = 28:72). Recrystallization from hexane/ethyl acetate (2:1, v/v) afforded pure **5b** diastereomer. White crystals; mp 198–199 °C; $[\alpha]_D = -138.5$ (*c* 2, $CHCl_3$); IR (KBr): 1678, 1709; TLC (toluene/ethanol 6:1): $R_f = 0.39$; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.75–1.91 (m, 2H, H-7, H′-7), 2.10–2.28 (m, 3H, H′-6, H-8, H′-8), 2.82 (m, 1H, $^2J = 8.5$, $^3J = 9.5$, $^3J = 2.4$, H-6), 3.19 (t, 1H, $^3J = 8.3$, H-8a), 4.05 (s, 1H, H-4), 7.34–7.43 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 7.89 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2 (C-7), 25.0 (C-8), 52.3 (C-6), 65.1 (C-8a), 71.8 (C-4), 128.9 (C-3′, C-5′), 129.0 (C-4′), 129.3 (C-2′, C-6′), 136.0 (C-1′), 171.5 (C-3), 172.4 (C-1); HRMS (ESI): $(M+H)^+$ calcd for $C_{13}H_{15}N_2O_2$, 231.1128; found, 231.1121.

4.4. X-ray crystallographic determination of compounds 4a and 5b

The crystal and molecular structures of **4a** and **5b** have been determined by X-ray diffraction. Crystals suitable for X-ray analysis were grown from hexane/ethyl acetate (2:1, v/v) solution by slow evaporation. Diffraction data were collected on an Oxford Diffraction KM4CCD diffractometer[29] for **4a** and on a KM4 KUMA diffractometer[30] for **5b** at 293 K, using graphite-monochromated Mo K_α ($\lambda = 0.71073$ Å) and Cu K_α ($\lambda = 1.54178$ Å) radiation for **4a** and **5b**, respectively. For **4a**, the accurate unit cell dimensions were obtained by the least-squares fit of setting angles of 12,852 highest-intensity reflections chosen from the whole experiment and for **5b** of setting angles of 41 reflections ($16° < 2\theta < 63°$). Intensity data were corrected for the Lorentz and polarization effects.[31,32] The structures were solved by direct methods by use SHELXS-97 program[33] and full-matrix, least-squares refinements on F^2 were performed by use of the SHELXL-97 program.[34] The function $\sum w(|F_o|^2 - |F_c|^2)^2$ was minimized with $w^{-1} = [\sigma^2(F_o)^2 + (0.0897P)^2]$ for **4a** and $w^{-1} = [\sigma^2(F_o)^2 + (0.1286P)^2 + 0.0845P]$ for **5b**, where $P = (F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined anisotropically, positions of hydrogen atoms were generated geometrically and refined as a riding model. Thermal parameters of all hydrogen atoms were calculated as 1.2 (1.5 for methyl group) times U_{eq} of the respective carrier carbon atom. An empirical extinction correction was also applied according to the formula $F_c' = kF_c[1 + (0.001\chi F_c^2\lambda^3/\sin 2\theta)]^{-1/4}$,[34] and the extinction coefficient χ was equal to 0.016(2) for **4a** and 0.026(6) for **5b**. The figures were drawn with MERCURY program.[35]

The deposition numbers CCDC 652248 for **4a** and 652249 for **5b** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

4.4.1. Crystal data for 4a. $C_{14}H_{18}N_2O_3$, $M = 262.30$, $D_c = 1.231$ g/cm^3, orthorhombic, $P2_12_12_1$, $a = 8.7828(3)$ Å, $b = 16.2593(6)$ Å, $c = 19.8168(7)$ Å, $V = 2829.9(2)$ Å^3, $Z = 8$, $F(000) = 1120$, $\mu = 0.087$ mm^{-1}. The reflections collected were 28,243 of which 7408 unique [$R(\text{int}) = 0.0286$]; 5439 reflections $I > 2\sigma(I)$, $R_1 = 0.0474$ and $wR_2 = 0.1327$ for 5439 [$I > 2\sigma(I)$] and $R_1 = 0.0658$ and $wR_2 = 0.1432$ for all (7408) intensity data. Goodness of

fit = 1.028, residual electron density in the final Fourier map was 0.288 and −0.151 e Å^{-3}.

4.4.2. Crystal data for 5b. $C_{13}H_{14}N_2O_2$, $M = 230.26$, $D_c = 1.290$ g/cm^3, monoclinic, $P2_1$, $a = 9.070(1)$ Å, $b = 5.8728(6)$ Å, $c = 11.983(1)$ Å, $\beta = 111.73(1)°$, $V = 592.9(1)$ Å^3, $Z = 2$, $F(000) = 1120$, $\mu = 0.719$ mm^{-1}. The reflections collected were 1407 of which 1344 unique [R(int) = 0.0803]; 1327 reflections $I > 2\sigma(I)$, $R_1 = 0.0551$ and $wR_2 = 0.1752$ for 1327 [$I > 2\sigma(I)$] and $R_1 = 0.0556$ and $wR_2 = 0.1761$ for all (1344) intensity data. Goodness of fit = 1.105, residual electron density in the final Fourier map was 0.208 and −0.280 e Å^{-3}.

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