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Stereoselective functionalization strategy of 2,5-diketopiperazine derived from L-proline and glycine

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Dedicated to Acad. Bogdan Kurtev on the occasion of his 100th birth anniversary

The functionalization of diketopiperazine Cyclo(Gly-Pro) by using suitable deprotonation reagent and electrophile offers the opportunity for synthesis of structurally diverse series of compounds (libraries) possessing bioactivity. This synthetic approach has been proved as feasible in respect to use different electrophiles and in particularly concerning the observed very high stereoselecitvity.

Key words: 2,5-diketopiperazines; alkylation; acylation; LHMDS; LDA

INTRODUCTION

Diketopiperazines (DKPs) are the smallest cyclic peptides in which the two nitrogen atoms of a piperazine 6-membered ring are part of amide linkages. Three regioisomers are possible, differing in the locations of the two carbonyl groups around the ring. All of these three isomeric diketo-piperazines, the 2,5-derivatives (Fig. 1) have attracted the greatest interest.

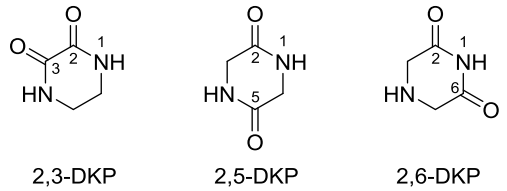

Fig. 1. Isomers of diketopiperazines.

The 2,5-DKPs occur in numerous natural products isolated from fungi, bacteria, plants and animals. Diketopiperazines are important for drug discovery due to their properties, such as conformationally constrained scaffolds, stability to proteolysis, ability to simulate peptidic pharmacophore groups and to bind to a wide range of biological targets. It is important to note that within the DKP framework, diversity can be introduced at up to six positions with stereochemical control at up to four positions. Recently published review articles describe their properties, biological activity and methods of synthesis [1–4]. Most of the natural and synthetic 2,5-DKPs exhibit different kinds of biological activity, *e.g.* antitumor [5–9], antiviral [10, 11], antifungal [12] and antibacterial [13, 14]. Important is their potential to be applied as neuroprotective agents [3, 15].

Our interest in the chemistry of diketopiperazines has been attracted by the recently isolated compound **A** (Fig. 2), which was isolated from the fungal culture *Leptoxyphium* sp. [16]. This compound has been evaluated as very promising inhibitor of monocyte chemotactic protein-1, which has been implicated in both acute and chronic inflammatory and autoimmune diseases, associated with infiltration of monocytes. Therefore, this compound has the potential to serve as a model for development of small molecular weight chemokine receptor antagonists as anticancer agents.

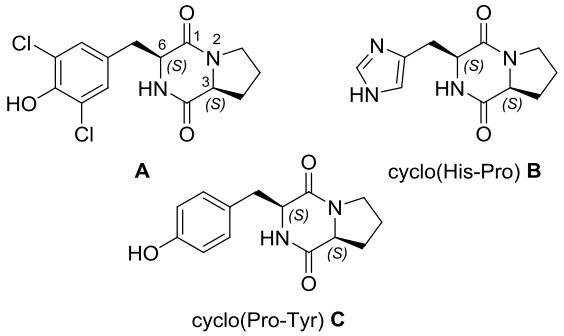

Fig. 2. 2,5-Diketopiperazines containing L-proline structural motif.

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The importance of the proline containing DKPs in the development of bioactive agents could be further demonstrated with the examples of Cyclo(His-Pro) **B** (obtained by enzymatic cleavage of the hypothalamic TRH (thyrotropin releasing hormone) [17], intensively investigated for its role in the CNS (central nervous system) [18–20]) and the fungal host-specific phytotoxin maculosin-1, cyclo(Pro-Tyr) **C**, produced by *Alternaria alternata* on spotted knapweed (*Centaurea maculosa*) (possible template for creating a safe and environmentally friendly specific bioherbicides [21]).

Inspired by this results we are describing our feasibility studies to develop approach for the preparation of compound **A**, which could be of general applicability for the synthesis of a series of structurally diverse analogues with control of the stereochemistry. Thus the synthesis of the N-benzyl protected diketopiperazine cyclo(Gly-Pro) was obtained from L-proline and glycine and the introduction of suitable substituents at 6-position of the ring was studied by means of deprotonation-coupling methodology.

EXPERIMENTAL

General

The reactions with air and moisture sensitive reagents were carried out in flame-dried Schlenk flasks under an argon atmosphere. The organic solvents were distilled prior to use. The THF was dried by refluxing over sodium/benzophenone and distilled under an argon atmosphere. Thin layer chromatography (TLC) was performed on aluminium sheets pre-coated with silica gel 60 F_{254} (Merck). Flash column chromatography was carried out using silica gel 60 (230–400 mesh, Merck). The melting points of the compounds were determined by using BOETIUS, type PHMK 05 (uncorrected). The NMR spectra were recorded in $CDCl_3$ on a Bruker Avance II+ 600 (600.13 MHz for ^{1}H NMR, 150.92 MHz for ^{13}C NMR) spectrometer with TMS as the internal standard for chemical shifts (δ, ppm). ^{1}H and ^{13}C NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration, and identification. The assignment of the ^{1}H and ^{13}C NMR spectra was made on the basis of DEPT, HSQC, and NOESY experiments. All assignments marked with an asterisk are tentative. Mass spectra (MS) were recorded on a Thermo Scientific DFS (Double Focusing Magnetic Sector) mass spectrometer using chemical ionization and reported as fragmentation in *m/z* with relative intensities (%) in parentheses and reported as fragmentation in *m/z* with relative intensities (%) in parentheses. Elemental analyses were performed by the Microanalytical Service Laboratory of the Institute of Organic Chemistry, Bulgarian Academy of Sciences.

The following commercially available starting materials were used: Benzyl bromide (*Aldrich*), NaH (60% dispersion in mineral oil, *Aldrich*), LHMDS (1 M solution in THF/ethylbenzene, *Acros*), LDA (2 M solution in THF/*n*-heptane/ethylbenzene, *Acros*), 3,5-dimethoxybenzyl bromide (*Aldrich*), 3-methylbenzoyl chloride (*Aldrich*).

*(S)-2-benzylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **7***

To a suspension of (*S*)-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**6**) (0.647 g, 4.196 mmol) in acetonitrile (220 ml) NaH (6.294 mmol) was added. The reaction mixture was stirred for 40 min. at 50 °C after that benzyl bromide (0.35 ml, 5.035 mmol) was added. After 24 h the solvent was evaporated, the residue was dissolved with CH_2Cl_2, the organic phase was washed with saturated solution of NaCl and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (φ = 28 mm, *h* = 530 mm, 70 g silica gel, eluent: CH_2Cl_2/CH_3OH = 40:1) to give 0.801 g (78%) of **7** as colorless crystals. R_f = 0.48 (eluent: EtOAc/CH_3OH = 10:1); mp 112–114 °C (Et_2O/petroleum ether). ^{1}H NMR ($CDCl_3$): δ = 7.23–7.38 (m, 5H, H_{ar}), 4.74 (d, *J* = 14.6, 1H, H-10), 4.46 (d, *J* = 14.4, 1H, H-10), 4.13 (m, 1H, H-3), 3.98 (d, *J* = 16.6, 1H, H-6), 3.76 (d, *J* = 16.6, 1H, H-6), 3.48–3.67 (m, 2H, H-9), 2.39–2.51 (m, 1H, H-7), 1.93–2.21 (m, 3H, H-7, H-8). ^{13}C NMR: δ = 167.15 (s, NC=O), 163.00 (s, NC=O), 135.44 (s, C-11), 128.91 (2d, C_{ar}), 128.33 (2d, C_{ar}), 128.06 (d, C-14), 59.08 (d, C-3), 51.13 (t, CH_2), 49.51(t, CH_2), 45.20 (t, CH_2), 29.00 (t, CH_2), 22.56 (t, CH_2).

*(8aS)-2-benzyl-3-(3,5-dimethoxybenzyl)hexahydro-pyrrolo[1,2-a]-pyrazine-1,4-dione **8***

Method A: To a solution of **7** (0.200 g, 0.819 mmol) in dry THF (10 ml) LHMDS (1.23 ml, 1.228 mmol) was added at -78 °C through a septum under Ar atmosphere. After 1 h 3,5-dimethoxybenzyl bromide (0.227 g, 0.982 mmol) dissolved in THF (2

ml) was added. After stirring for 3 h at -78 °C the temperature was allowed to rise to room temperature (20 °C) for 24 h. The mixture was quenched (aq. NH_4Cl), extracted with CH_2Cl_2, washed with water, and the organic phase was dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (φ = 20 mm, *h* = 530 mm, 50 g silica gel, eluent: EtOAc) to give 0.230 g (71%) of **8** as a light yellow oil. The isolated product **8** is a mixture of two diastereoisomers (**A** and **B**) in a ratio 95:5 (NMR data). The oil was crystallized from Et_2O/ petroleum ether to give colorless crystals, which are again mixture of two diastereoisomers (**A** and **B**) in a ratio 96:4 (NMR data).

Method B: To a solution of **7** (0.180 g, 0.737 mmol) in dry THF (10 ml) LDA (0.74 ml, 1.474 mmol) was added at -78 °C through a septum under Ar atmosphere. After 1 h 3,5-dimethoxybenzyl bromide (0.227 g, 0.982 mmol) dissolved in THF (2 ml) was added. After stirring for 4 h at -78 °C the temperature was allowed to rise to room temperature (20 °C) for 24 h. The mixture was quenched (aq. NH_4Cl), extracted with CH_2Cl_2, washed with water, and the organic phase was dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (φ = 20 mm, *h* = 530 mm, 50 g silica gel, eluent: EtOAc) to give 0.134 g (55%) of the **8** as a light yellow oil. The isolated product **8** is a mixture of two diastereoisomers (**A** and **B**) in a ratio 95:5 (NMR data). R_f = 0.53 (eluent: EtOAc, the two diastereoisomers have the same R_f-value in different solvents or mixture of solvents), mp = 106–108 °C (PE/Et_2O; mixture of two diastereoisomers in ratio 96:4). ^{1}H NMR: δ = 7.23–7.33 (m, 3H, H-12, H-14, H-16), 7.20–7.21 (m, 2H, H-13, H-15), 6.39 (t, *J* = 2.3, 1H, H-21$_{\text{isomer A}}$), 6.35 (t, *J* = 2.3, 1H, H-21$_{\text{isomer B}}$), 6.25 (d, *J* = 2.2, 2H, H-19$_{\text{isomer A}}$, H-23$_{\text{isomer A}}$), 6.23 (d, *J* = 2.2, 2H, H-19$_{\text{isomer B}}$, H-23$_{\text{isomer B}}$), 5.70 (d, *J* = 14.7, 1H, H-10$_{\text{isomer B}}$), 5.27 (d, *J* = 14.8, 1H, H-10$_{\text{isomer A}}$), 4.2 (t, *J* = 3.8, 1H, H-6$_{\text{isomer B}}$), 4.15 (t, *J* = 4.7, 1H, H-6$_{\text{isomer A}}$), 4.02 (d, *J* = 14.7, 1H, H-10$_{\text{isomer B}}$), 3.87 (d, *J* = 14.7, 1H, H-10$_{\text{isomer A}}$), 3.74 (s, 6H, 2OCH_3), 3.58 (dt, *J* = 12.2, 8.5, 1H, H-9), 3.36 (m, 1H, H-9), 3.07 (d, *J* = 4.90, 2H, H-17), 2.90 (dd, *J* = 10.7, 6.4, 1H, H-3), 2.20–2.25 (m, 1H, H-7), 1.92–1.96 (m, 1H, H-8), 1.80–1.85 (m, 1H, H-7), 1.65–1.69 (m, 1H, H-8). ^{13}C NMR: δ = 167.65 (s, NC=O), 164.87 (s, NC=O), 160.89 (2s, C-20, C-22), 137.44* (s, C-11), 135.89* (s, C-18), 128.92 (2d, C-12, C-16), 128.45 (2d, C-13, C-15), 128.05 (d, C-14), 107.48 (2d, C-19, C-23), 99.99 (d, C-21), 62.45 (d, C-6), 57.92 (d, C-3), 55.43 (2q, 2OCH_3), 47.38 (t, C-10), 44.98 (t, C-9), 37.22 (t, C-17), 29.38 (t, C-7), 21.94 (t, C-8). MS (CI) *m/z* = 395 (100, $[M+1]^+$), 243 (90), 90 (55). Anal. Calcd for $C_{23}H_{26}N_2O_4$ (394.471): C 70.03, H 6.64, N 7.10; Found: C 69.74, H 6.95, N 7.19.

*(8aS)-2-benzyl-3-(3-methylbenzoyl)hexahydro-pyrrolo[1,2-a]-pyrazine-1,4-dione **9** and 2-benzyl-8a-(3-methylbenzoyl)hexahydropyrrolo[1,2-a] pyrazine-1,4-dione **10***

Method A: To a solution of **7** (0.200 g, 0.819 mmol) in dry THF (10 ml) LHMDS (1.23 ml, 1.228 mmol) was added at -78 °C through a septum under Ar atmosphere. After 1 h 3-methylbenzoyl chloride (0.13 ml, 0.982 mmol) was added portion wise for a period of 15 min. After stirring for 3 h at -78 °C the temperature was allowed to rise to room temperature (20 °C) for 24 h. The mixture was quenched (aq. NH_4Cl), extracted with CH_2Cl_2, washed with water, and the organic phase was dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (φ = 20 mm, *h* = 530 mm, 50 g silica gel, eluent: CH_2Cl_2/Et_2O = 15:1) to give 0.075 g (25%) of **9** (colorless crystals), as single diastereoisomer. R_f = 0.54 (eluent: $EtOAc/CH_3OH$ = 40:1); mp = 153–155 °C (PE/Et_2O). ^{1}H NMR: δ = 7.89 (d, *J* = 7.80, 1H, H-23), 7.86 (s, 1H, H-19), 7.41 (dt, *J* = 8.22, 0.66, 1H, H-21), 7.34 (t, *J* = 7.68, 1H, H-22), 7.23–7.25 (m, 3H, H-13, H-14, H-15), 7.15 (m, 2H, H-12, H-16), 5.50 (s, 1H, H-6), 5.03 (d, *J* = 14.80, 1H, H-10), 4.33 (dd, *J* = 10.26, 6.84, 1H, H-3), 4.06 (d, *J* = 14.80, 1H, H-10), 3.58–3.62 (m, 1H, H-9), 3.39–3.43 (m, 1H, H-9), 2.48–2.52 (m, 1H, H-7), 2.40 (s, 3H, H-24), 2.07–2.14 (m, 1H, H-7), 1.99–2.05 (m, 1H, H-8), 1.81–1.89 (m, 1H, H-8). ^{13}C NMR: δ = 191.17 (s, C=O), 169.44 (s, NC=O), 159.51 (s, NC=O), 138.63* (s, C-11), 135.42 (d, C-21), 135.00* (s, C-18), 133.85* (s, C-20), 130.03 (d, C-19), 128.89 (4d, C-12, C-13, C-15, C-16), 128.63 (d, C-22), 128.16 (d, C-14), 127.09 (d, C-23), 67.91 (d, C-6), 59.46 (d, C-3), 49.08 (t, C-10), 46.13 (t, C-9), 29.47 (t, C-7), 22.60 (t, C-8), 21.35 (q, CH_3). MS (CI) *m/z* = 363 (78, $[M+1]^+$), 119 (100). Anal. Calcd for $C_{22}H_{22}N_2O_3$ (362.429): C 72.91, H 6.12, N 7.73; Found: C 73.15, H 6.33, N 7.97.

Method B: To a solution of **7** (0.150 g, 0.614 mmol) in dry THF (10 ml) LDA (0.61 ml, 1.228 mmol) was added at -78 °C through a septum under Ar atmosphere. After 1 h 3-methylbenzoyl chloride

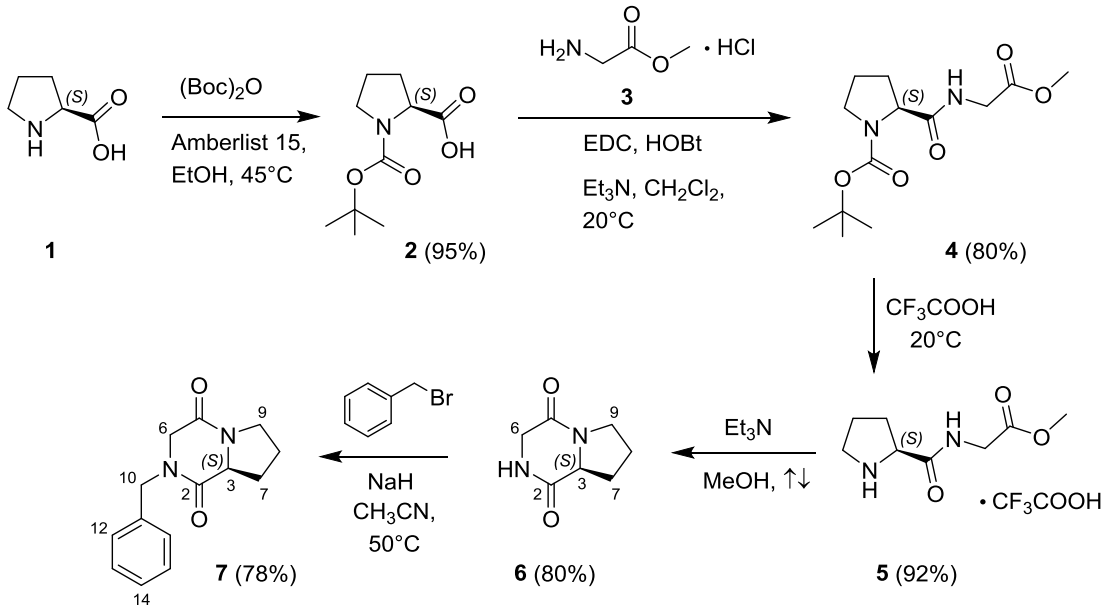
(0.18 ml, 1.351 mmol) was added portion wise for a period of 10 min. After stirring for 3 h at -78 °C the mixture was quenched (aq. NH_4Cl), extracted with CH_2Cl_2, and washed with water and the organic phase was dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (φ = 20 mm, *h* = 530 mm, 50 g silica gel, eluent: PE/Et_2O = 1:4). It was isolated 0.058 g (26%) of product **9** and 0.019 g (9%) of product **10** as light yellow oil. The data of **9** are identical with those obtained using LHMDS as a deprotonating agent.

Data for **10**: R_f = 0.45 (eluent: EtOAc/CH_3OH = 40:1). ^{1}H NMR: δ = 8.15 (d, *J* = 7.80, 1H, H-23), 8.04 (d, 1H, H-19), 7.44 (d, *J* = 7.56, 1H, H-21), 7.38 (t, *J* = 7.74, 1H, H-22), 7.19–7.22 (m, 1H, H-14), 7.15–7.19 (m, 2H, H-13, H-15), 6.93–6.94 (m, 2H, H-12, H-16), 4.71 (d, *J* = 14.70, 1H, H-10), 4.35 (d, *J* = 14.70, 1H, H-10), 3.82 (d, *J* = 17.04, 1H, H-6), 3.72–3.76 (m, 1H, H-9b), 3.69 (d, *J* = 17.04, 1H, H-6), 3.47–3.51 (m, 1H, H-9), 3.01–3.06 (m, 1H, H-7), 2.68–2.72 (m, 1H, H-7), 2.43 (s, 3H, H-24), 1.95–2.01 (m, 1H, H-8), 1.73–1.81 (m, 1H, H-8). ^{13}C NMR: δ = 193.02 (s, C=O), 165.09 (s, NC=O), 165.05 (s, NC=O), 138.60* (s, C-11), 135.20* (s, C-18), 134.91 (d, C-21), 132.71* (s, C-20), 130.65 (d, C-19), 128.88 (2d, C-13, C-15), 128.51 (d, C-22), 127.98 (d, C-14), 127.82 (2d, C-12, C-16), 127.60 (d, C-23), 77.39 (s, C-3), 51.77 (t, C-6), 50.53 (t, C-10), 44.81 (t, C-9), 33.71 (t, C-7), 21.99 (t, C-8), 21.45 (q, CH_3). MS (CI) *m/z* = 363 (100, $[M+1]^+$), 243 (47), 119 (68), 91 (47). Anal. Calcd for $C_{22}H_{22}N_2O_3$ (362.429): C 72.91, H 6.12, N 7.73; Found: C 72.64, H 5.89, N 7.53.

RESULTS AND DISCUSSION

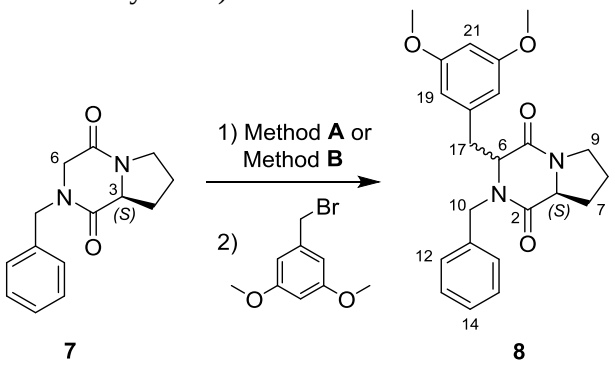
The unsubstituted diketopiperazine Cyclo(Gly-Pro) **6** was synthesized according published procedure over 4 steps (Scheme 1) without purification of the intermediates [22]. However, we could significantly improve the overall yield of **6** to 56% starting with L-proline **1**, compared with the published yield of 38% for the reaction sequence from **2** to **6**. The N-benzylation of **6** occurred by using NaH, benzylbromide in acetonitrile in 78% yield and it was curious that we could not found this procedure in the literature. The synthesis of compound **7** has been described to proceed in 56% yield by multicomponent Ugi-reaction, however without taking into account the yield for preparation of one of the starting compounds that needs 5-step procedure [23].

The N-benzylated DKP **7** was used as starting compound for the planned experiments. For the deprotonation of **7** the reagents lithium hexamethyldisilazide (LHMDS) and lithium diisopropyl amide (LDA) were used (Scheme 2). The alkylation of the generated enolate was realized with 3,5-dimethoxybenzyl bromide as a model compound, since 3,5-dichloro-4-hydroxybenzyl bromide, needed for the synthesis of DKP **A** was not commercially available. The reaction sequence using LHMDS leading to DKP **8** was high yielding, whereas with LDA a moderate yield could be realized.



Scheme 1. Synthesis of the Cyclo(Gly-Pro) **6** and the N-benzylated DKP **7**.

In both cases an excellent diastereoselectivity was observed. One crystallization from diethyl ether/petroleum ether could not improve the diastereoisomeric ratio (**8a**:**8b** = 96:4-ratio was observed by NMR).



Method **A**: LHMDS 71% **8a**:**8b** = 95:5 (90% de)
Method **B**: LDA 55% **8a**:**8b** = 95:5 (90% de)

Scheme 2. Alkylation of **7** with 3,5-dimethoxybenzyl bromide using LHMDS (Method **A**) or LDA (Method **B**) as deprotonating agents (the numbering of the C-atoms is presented to support the assignment of the NMR spectra).

The configuration of the newly formed stereogenic center in the major diastereoisomer **8a** was determined by using advanced NMR experiments. Important prerequisite was the rigid structure of the 2,5-diketopiperazine ring fused to the cyclic five-membered proline-ring resulting in a stable boat conformation of the DKP [24, 25]. For determining the configuration at the stereogenic center C-6 it was necessary to identify the relative position of the 3,5-dimethoxybenzyl moiety attached. By means of NOESY spectra the proton proximities shown with arrows in Fig. 3 were observed (only most important proton-proton NOE interdependencies are presented). The observed proximities between the formal proline proton at the C-3 position of the DKP-ring and the *ortho*-proton of the 3,5-dimethoxybenzyl moiety, as well as the positions of protons from the both benzylic CH_2-groups relative to those of the C-6 proton, allowed to deduce the configuration of C-6 stereogenic center as ***R*** taking into account the known ***S*** configuration of C-3. Consequently, the major diastereoisomer of compound **8** is formed as a result of the reaction between deprotonated DKP **7** and 3,5-dimethoxybenzyl bromide approaching from the less hindered opposite direction relative to the tilt between the proline and DKP fused rings.

As next aim in the feasibility study was proved and tested the reaction of deprotonated **7** with 3-methylbenzoyl chloride (Scheme 3). Irrespective of the deprotonation agent (LHMDS or LDA) the expected product **9** could be isolated after chromatography purification in low yield (25%).

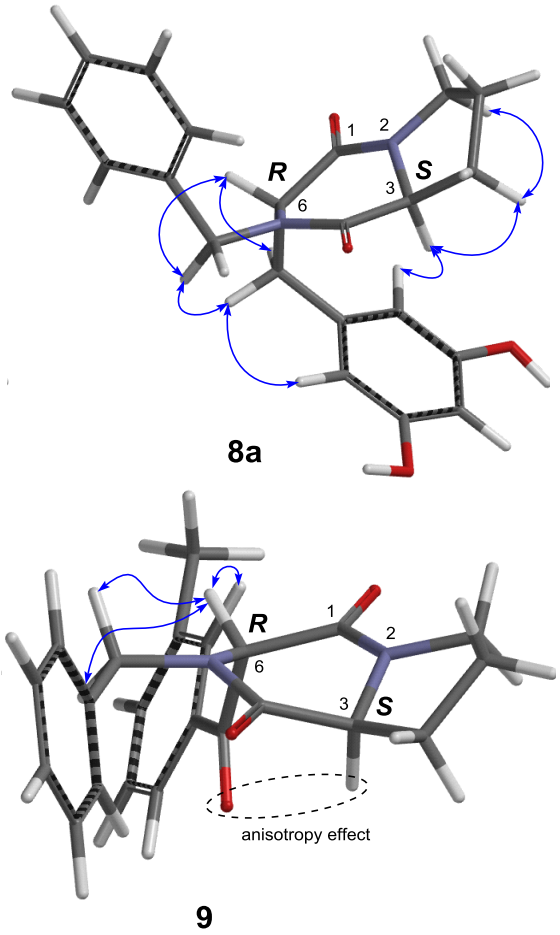
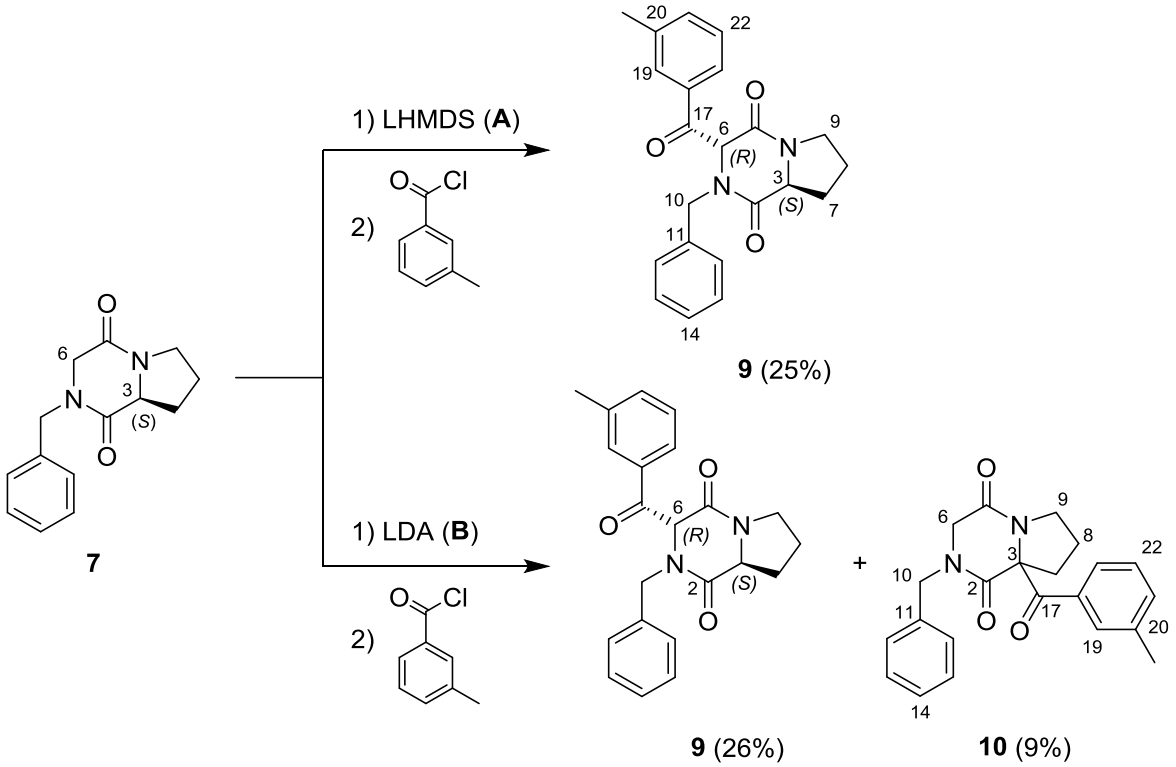


Fig. 3. The observed proton proximities by means of NOESY spectra used for determination of the configuration of compounds **8a** (major diastereoisomer) and **9**.

Surprisingly, in the reaction performed with LDA the formation of the by-product **10** was observed (9% yield of isolated compound). Compounds **9** and **10** could be separated by column chromatography and isolated in pure form. It is noteworthy that compound **9** was formed as a single diastereoisomer. The stereoselectivity was expected to be the same as in the case of compound **8**. The most significant argument for the configuration of **9** was the chemical shift of the C-3 proton (4.33 ppm), which was downfield shifted compared with the same proton in compound **8a** (2.90 ppm). This observation was obviously a result of the anisotropy effect and the corresponding deshielding of C-3 proton. The observed proton proximities in the NOESY spectra (Fig. 3) supported the suggested configuration for the C-6 stereogenic center as ***R***. The NMR spectra of



Scheme 3. Acylation of **7** with 3-methylbenzoyl chloride using LHMDS (Method **A**) or LDA (Method **B**) as deprotonating agents (the numbering of the C-atoms is presented to support the assignment of the NMR spectra).

compound **10** (1D and 2D) clearly supported the structure presented in Scheme 3. At this moment the discussion about the formation of **10** would be speculative.

CONCLUSION

The feasibility of the reaction sequence deprotonation of diketopiperazine Cyclo(Gly-Pro) followed by reaction with electrophiles proved to be a promising strategy for synthesis of libraries of structurally diverse compounds possessing biological activity. The observed stereoselectivity is significant advantage in the synthesis of compounds with definite configuration.

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СТРАТЕГИЯ ЗА СТЕРЕОСЕЛЕКТИВНО ФУНКЦИОНАЛИЗИРАНЕ НА 2,5-ДИКЕТОПИПЕРАЗИН ПОЛУЧЕН ОТ L-ПРОЛИН И ГЛИЦИН

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(Резюме)

Функционализирането на дикетопиперазин Cyclo(Gly-Pro) чрез използване на подходящ депротониращ реагент и електрофил предлага възможността за синтез на структурно разнообразни серии от съединения (библиотеки), притежаващи биоактивност. Този синтетичен подход беше доказан, че е осъществим по отношение на използване на разнообразни електрофили и особено относно наблюдаваната висока стереоселективност.