

# Stereoselectivity during a Dieckmann Analogous Cyclization of (Piperazin-2-yl)propionic Acid Esters

Christian Geiger<sup>a</sup>, Christel Zelenka<sup>a</sup>, Roland Fröhlich<sup>b</sup>, Birgit Wibbeling<sup>b</sup>, and Bernhard Wünsch<sup>a</sup>

<sup>a</sup> Institut für Pharmazeutische und Medizinische Chemie der Westfälischen Wilhelms-Universität Münster, Hittorfstraße 58-62, D-48149 Münster, Germany

<sup>b</sup> Organisch-Chemisches Institut der Westfälischen Wilhelms-Universität Münster, Corrensstr. 40, D-48149 Münster, Germany

Reprint requests to Prof. Dr. B. Wünsch. E-mail: wuensch@uni-muenster.de

Z. Naturforsch. **60b**, 1068 – 1070 (2005); received July 4, 2005

*Dedicated to Prof. Dr. A. W. Frahm on the occasion of his 70<sup>th</sup> birthday*

The primary Dieckmann cyclization product of the methyl (3,6-dioxopiperazin-2-yl)propionate was trapped with chlorotrimethylsilane and recrystallized. The X-ray crystal structure analysis showed (*S*)-configuration of the novel chiral centre. This configuration supports the hypothesis that formation of the stable lithium chelate is responsible for shifting this unusual Dieckmann cyclization towards the bicyclic product.

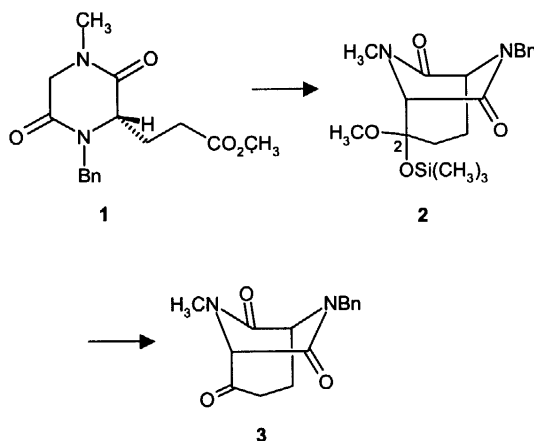
**Key words:** X-Ray Crystal Structure Analysis, Dieckmann Cyclization, Bridged Piperazines, Stereochemistry

## Results

Recently we have described that methyl (3,6-dioxopiperazin-2-yl)propionate (**1**) undergoes a variation of the Dieckmann cyclization which proceeds by trapping of the primarily formed hemiacetal anion by chlorotrimethylsilane to give the mixed methyl silyl acetal **2** of the bicyclic ketone **3**. After careful hydrolysis the desired Dieckmann condensation product, the ketone **3**, was obtained in good yields. Standard reaction conditions, which are usually employed for the Dieckmann condensation, failed to give the ketone **3** [1, 2].

Usually, the driving force shifting the equilibrium towards the cyclization product is the deprotonation of the formed  $\beta$ -ketoester [3]. After cyclization of **1** to **3** a proton at a bridgehead carbon would have to be removed to obtain an enolate anion. This deprotonation is not allowed in the case of **3** according to Bredt's rule [4], which explains the failure of the Dieckmann cyclization under equilibrium conditions.

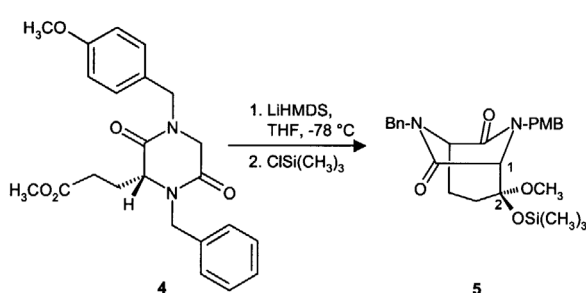
Surprisingly the mixed methyl silyl acetal **2** was formed with an extraordinarily high stereoselectivity during our cyclization method, and the corresponding diastereomeric methyl silyl acetal could not be detected. However, it was not possible to unambiguously determine the configuration of the novel centre of chi-



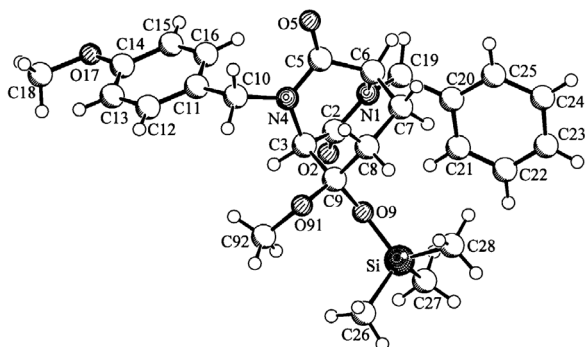
Scheme 1.

ality by various NMR techniques (HSQC, NOE, C/H-COSY).

In order to study relationships between the structure and the  $\sigma$ -receptor affinity within the class of bridged piperazines, we investigated the cyclization of the 4-(*p*-methoxybenzyl)piperazine derivative **4**, which is derived from (*R*)-glutamate [5]. According to the described Dieckmann cyclization protocol the propionic acid ester **4** was treated with 1.10 equivalents of LiHMDS (lithium hexamethyldisilazane) at  $-78^\circ\text{C}$



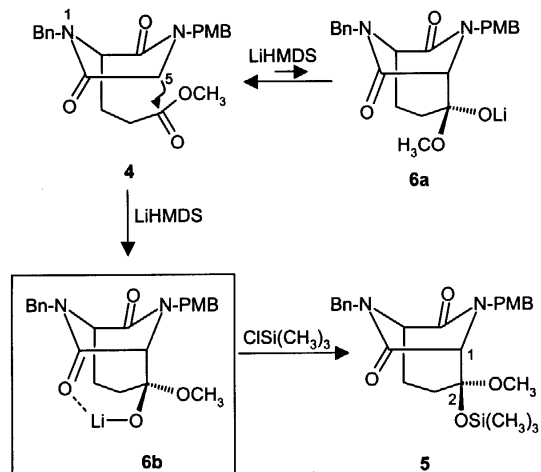
Scheme 2.

Fig. 1. ORTEP plot of the X-ray structure analysis of **5**.

and after 30 min at low temperature the initial product was trapped with chlorotrimethylsilane. This reaction provided only one stereoisomerically pure product **5** in 96% yield. Recrystallization of the methyl silyl acetal **5** from methanol/water 1:1 proceeded to provide colourless crystals which were suitable for X-ray crystal structure analysis.

The X-ray crystal structure analysis revealed the rel-(1*R*,2*S*) configuration of **5**. Since the synthesis of the methyl propionate **4** started with the enantiomerically pure amino acid (*R*)-glutamate, the absolute configuration 2*S* was confirmed by the X-ray crystal structure analysis.

The (*S*)-configuration of the mixed methyl silyl acetal **5** supports our hypothesis on the reaction course: We assume that the piperazinedione **4** is deprotonated in position 5 to afford an anion which reacted with the ester moiety. The planar carbonyl moiety of the ester group can be attacked from the *si*- and *re*-side to provide the diastereomeric hemiacetal anions **6a** and **6b**, respectively. Whereas the anion **6a** is in equilibrium with the ring-opened piperazinedione anion, the lithium alcoholate **6b** is stabilized in a six-membered chelate. The formation of the chelate **6b** is the driving force, which shifts the equilibrium almost quantitatively towards the Dieckmann cyclization product,



Scheme 3.

which is finally silylated with chlorotrimethylsilane. If the equilibrium was not shifted towards **6b**, trapping with chlorotrimethylsilane would result in further silylated products.

## Experimental Section

### General

Melting points: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. – Optical rotation: Polarimeter 341 (Perkin Elmer); 1.0 dm tube; concentration *c* (g/100 ml); temperature 20 °C. – Elemental analysis: Vario EL (Elementaranalysesysteme GmbH). – MS: MAT GCQ (Thermo-Finnigan); TSQ 7000 (Thermo-Finnigan); LCQ MAT (Thermo Finnigan); EI = electron impact. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). <sup>1</sup>H NMR (400 MHz): Unity Mercury Plus 400 NMR spectrometer (Varian);  $\delta$  in ppm related to tetramethylsilane.

(1*R*,2*S*,5*R*)-6-Benzyl-2-methoxy-8-(4-methoxybenzyl)-2-(trimethylsiloxy)-6,8-diazabicyclo-[3.2.2]nonane-7,9-dione (**5**)

Under nitrogen at –78 °C a solution of lithium hexamethyldisilazane (1 M in THF, 8.9 ml, 8.9 mmol) was added dropwise to a solution of **4** [**5**] (3.20 g, 7.79 mmol) in dry THF (70 ml). After 30 min of stirring at –78 °C a solution of chlorotrimethylsilane (3.6 ml, 28.36 mmol) in dry THF (10 ml) was added and the reaction mixture was stirred for 30 min at –78 °C and for 16 h at room temperature. Then, the solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate (80 ml), and the organic layer was washed with HCl (0.5 M) and NaOH (0.5 M), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to furnish **5** (3.60 g, 96%) as a viscous oil. IR (neat):  $\nu$  = 1681 (C=O amides), 1246, 1018 (each C–O–C), 1105, 872 (each O–Si), 843 cm<sup>–1</sup> (Si(CH<sub>3</sub>)<sub>3</sub>). – <sup>1</sup>H NMR

(CDCl<sub>3</sub>):  $\delta$  = 0.09 (s, 9 H, Si(CH<sub>3</sub>)<sub>3</sub>), 1.36–1.48 (m, 1 H, 4-H), 1.71–1.89 (m, 3 H, 3-H, 4-H), 3.12 (s, 3 H, OCH<sub>3</sub>), 3.71 (s, 3 H, PhOCH<sub>3</sub>), 3.81 (dd,  $J$  = 5.7/1.8 Hz, 1 H, 5-H), 3.86 (d,  $J$  = 14.8 Hz, 1 H, NCH<sub>2</sub>Ph), 3.87 (s, 1 H, 1-H), 4.32 (d,  $J$  = 14.7 Hz, 1 H, NCH<sub>2</sub>Ph), 4.58 (d,  $J$  = 14.7 Hz, 1 H, NCH<sub>2</sub>Ph), 5.09 (d,  $J$  = 14.7 Hz, 1 H, NCH<sub>2</sub>Ph), 6.77 (d,  $J$  = 8.6 Hz, 2 H, aromat. 3-H, 5-H<sub>methoxybenzyl</sub>), 7.04 (d,  $J$  = 8.6 Hz, 2 H, aromat. 2-H, 6-H<sub>methoxybenzyl</sub>), 7.14–7.27 (m, 5 H, aromat. H). – MS (EI):  $m/z$  (%) = 482 [M<sup>+</sup>, 41], 121 [CH<sub>2</sub>PhOCH<sub>3</sub><sup>+</sup>, 100], 91 [CH<sub>2</sub>Ph<sup>+</sup>, 48]. The oily product was triturated under a mixture of petroleum ether and methanol to yield a colorless solid, which was recrystallized from methanol-water (1:1) to give colorless crystals suitable for X-ray crystal structure analysis. M. p. 95 °C.  $[\alpha]_{589}$  = +8.7, ( $c$  1.72, CH<sub>2</sub>Cl<sub>2</sub>). – C<sub>26</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub>Si (482.6): calcd. C 64.7, H 7.10, N 5.80; found C 64.6, H 7.06, N 5.80.

#### X-ray crystal structure analysis of **5**

Formula C<sub>26</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub>Si,  $M$  = 482.64, colorless crystal 0.20 × 0.05 × 0.03 mm,  $a$  = 10.282(1),  $b$  = 11.960(1),  $c$  = 21.403(1) Å,  $V$  = 2632.0(4) Å<sup>3</sup>,  $\rho_{\text{calcd.}}$  = 1.218 g cm<sup>−3</sup>,  $\mu$  = 10.94 cm<sup>−1</sup>, empirical absorption correction (0.811 ≤  $T$  ≤ 0.968),  $Z$  = 4, orthorhombic, space group  $P2_12_12_1$  (no. 19),  $\lambda$  = 1.54178 Å,  $T$  = 223 K,  $\omega$  and  $\phi$  scans, 5904

reflections collected ( $h, \pm k, \pm l$ ),  $[(\sin \theta)/\lambda]_{\text{max}}$  = 0.59 Å<sup>−1</sup>, 2474 independent ( $R_{\text{int}}$  = 0.068) and 1389 observed reflections [ $I \geq 2\sigma(I)$ ], 312 refined parameters,  $R$  = 0.055,  $wR^2$  = 0.101, max. residual electron density 0.22 (−0.18) e Å<sup>−3</sup>, Flack parameter 0.05(6), hydrogens calculated and refined as riding atoms. Due to the small crystal size the diffracting power was weak and the completeness of reflection data is low. The data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT [6], data reduction Denzo-SMN [7], absorption correction Denzo [8], structure solution SHELXS-97 [9], structure refinement SHELXL-97 [10], graphics SCHAKAL [11].

CCDC-276363 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, E-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)].

#### Acknowledgements

Financial support of this work by the Fonds der Chemischen Industrie is gratefully acknowledged. Thanks are also due to the Degussa AG for donation of chemicals.

- 
- |   |  |
|---|--|
| <p>[1] M. Weigl, B. Wünsch, <i>Org. Lett.</i> <b>2</b>, 1177 (2000).<br/>         [2] M. Weigl, S. Bedürftig, C. A. Maier, B. Wünsch, <i>Bioorg. Med. Chem.</i> <b>10</b>, 2245 (2002).<br/>         [3] J. P. Schaefer, J. J. Blomfield, <i>Org. React.</i> <b>15</b>, 1 (1967).<br/>         [4] P. M. Warner, <i>Chem. Rev.</i> <b>89</b>, 1067 (1989).<br/>         [5] M. Weigl, B. Wünsch, <i>Tetrahedron</i> <b>58</b>, 1173 (2002).<br/>         [6] B. V. Nonius, Delft, The Netherlands (1998).</p> | <p>[7] Z. Otwinowski, W. Minor, <i>Methods in Enzymology</i> <b>276</b>, 307 (1997).<br/>         [8] Z. Otwinowski, D. Borek, W. Majewski, W. Minor, <i>Acta Crystallogr.</i> <b>A59</b>, 228 (2003).<br/>         [9] G. M. Sheldrick, <i>Acta Crystallogr.</i> <b>A46</b>, 467 (1996).<br/>         [10] G. M. Sheldrick, Universität Göttingen (1997).<br/>         [11] E. Keller, Universität Freiburg (1997).</p> |
|---|--|