

MCR 6: CHIRAL 2,6-PIPERAZINEDIONES VIA UGI REACTIONS WITH α -AMINO ACIDS, CARBONYL COMPOUNDS, ISOCYANIDES AND ALCOHOLS

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Dedicated to Prof. Dr. Koji Nakanishi to his 75th birthday

Abstract - A simple one-pot reaction based on the well known Ugi reaction for the generation of 2,6-piperazindiones is described, involving the multicomponent reaction of α -amino acids, carbonyl compounds, isocyanides and alcohols.

Recently, we published a very effective variation of the well-known Ugi reaction (U-4CR),¹ the five-center-four-component reaction (U-5C-4CR).²⁻⁵ This one-pot multicomponent reaction (MCR)⁶ combines very high yields (usually more than 95 %) and excellent stereoselectivity (d.e. $\approx$ 80 %) with simple preparative procedures.

α -Amino acids serve as difunctional educts in the U-5C-4CR instead of the amine and acid components in the familiar U-4CR. They react with equimolar amounts of aldehyde and isocyanide as well as with the alcohol which also serves as a solvent. After a reaction time of one hour to two days the product, a 1,1'-iminodicarboxylic acid derivative, is obtained in almost quantitative yield. 1,1'-Iminodicarboxylic acids and their derivatives constitute an interesting and well investigated group of natural substances. They can be isolated from several types of poisonous mushrooms.⁷ Opines,⁸ such as octopine and nepaline, which can be isolated from crown gall tumors, also belong to this class of compounds. 1,1'-Iminodicarboxylic acid derivatives are also pharmaceutically active as ACE-inhibitors.⁹

The preparative simplicity and the high yield of the U-5C-4CR makes it an ideal access to this interesting group of compounds.

The postulated reaction mechanism of the U-5C-4CR is given in **Figure 1**. First, the amino function of the α -amino acid (**1**) condenses with the aldehyde compound (**2**) to form the corresponding imine (**3**).

After α -addition of the isocyanide (4) to 3 an O-acylamide (5) is formed. By a nucleophilic attack of the alcohol (6) (fourth component, fifth reacting center), at the carboxylic carbon and a subsequent rearrangement the U-5C-4CR product a 1,1'-iminodicarboxylic acid derivative (7), is formed. The acid function of the α -amino acid is esterified with the solvent alcohol. In analogy to the U-4CR, a secondary amide is formed by the isocyanide. A new stereocentre is created at the prochiral carbonyl carbon atom of the aldehyde. Its preferred absolute configuration is induced by the employed chiral amino acid.

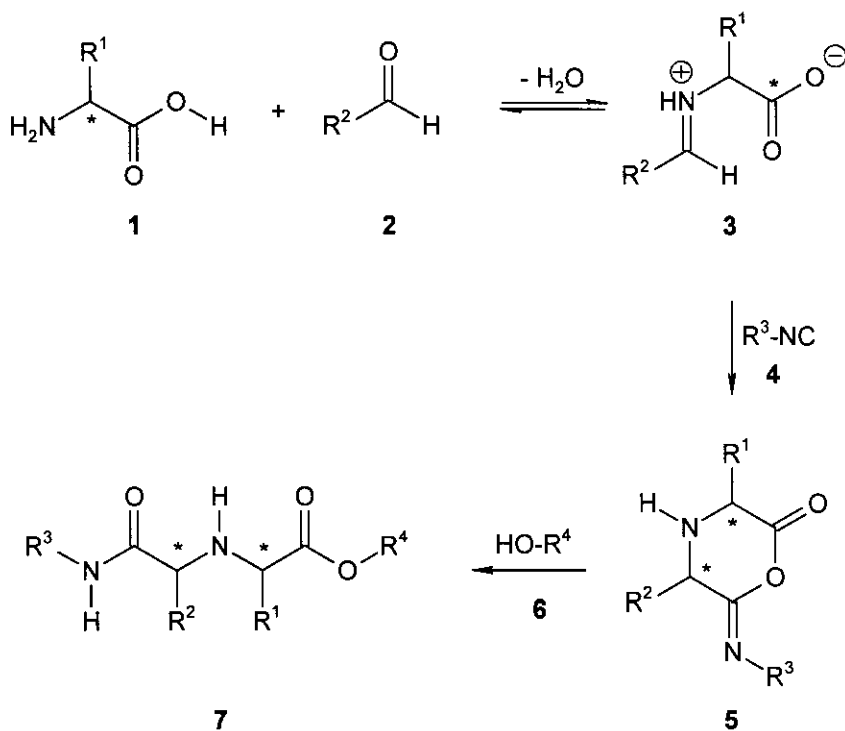


Figure 1: Postulated reaction mechanism of the U-5C-4CR.

The U-5C-4CR, as well as the U-4CR, is a very powerful tool for generating chemical libraries in liquid^{10,11} and on solid phase.^{3,12} The MCRs are more appropriate to achieve high degree of diversity and target specificity than any other chemical reaction known so far. A small number of different compounds can simply be mixed to create libraries directly as I. Ugi published in *Isonitrile Chemistry*¹ in 1971: "If, for example, 40 each of the different components are reacted with one other, the result [of the U-4CR] is $40^4 = 2,560,000$ reaction products, which is...of the same order of magnitude as the total number of chemical compounds described to date."

In the case of the U-5C-4CR the scope is only limited by the number of α -amino acids. There is no observed limitation of the U-5C-4CR by the isocyanides and the aldehydes in approx. 400 tested cases. It is also possible to bring different nucleophiles like prim. and sec. amines, thioles, and hydroxy ions to reaction.³

Because the U-5C-4CR is not limited to aldehydes as a carbonyl compound, it is possible to bring ketones to reaction. Due to the low reaction velocity of ketones in comparison to the aldehydes, the reaction time increases from approx. one day up to several weeks. Some products are given in **Figure 2**.

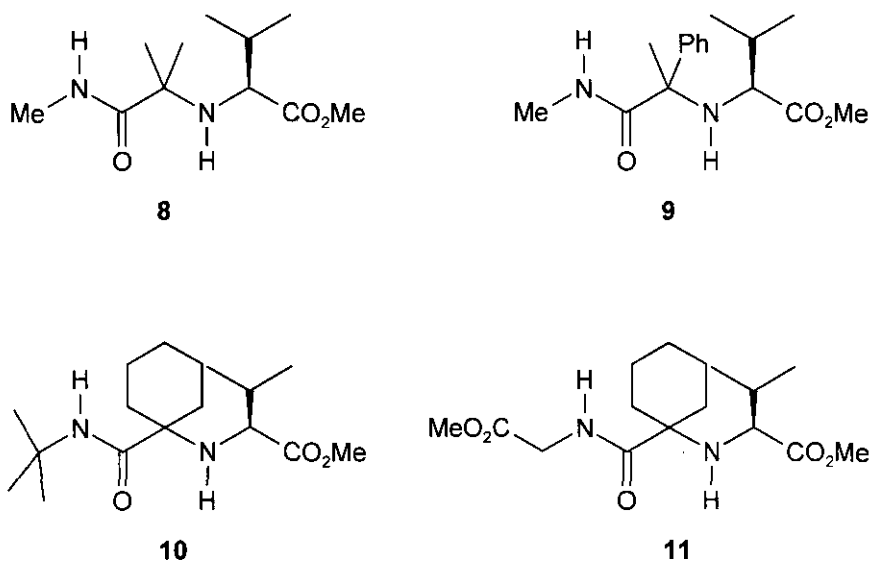


Figure 2: Examples of U-5C-4CR products of ketones

The reaction time of this MCR can be shortened by using higher temperatures and by adding a molequivalent triethylamine to increase the solubility of the unprotected amino acid in the corresponding alcohol. In the latter case the result is not only a shorter reaction time but also a secondary reaction, which leads not to the 1,1'-iminodicarboxylic acids derivatives but, in yields up to 85 %, to 2,6-piperazinediones, products of a intermolecular substitution of the ester by the sec. amide (**Figure 3**).

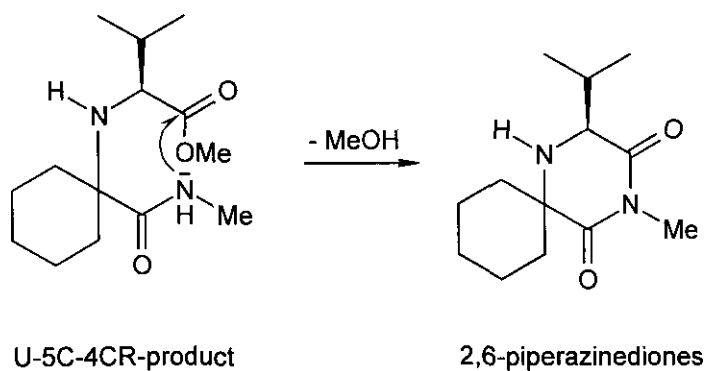


Figure 3: Mechanism of formation of 2,6-piperazinediones

The following examples for 2,6-piperazindiones shall document the broad possibilities of this variation. By using cyclic ketones it opens an elegant way to synthesize complex heterocyclic spiro-compounds through one-pot-reactions.

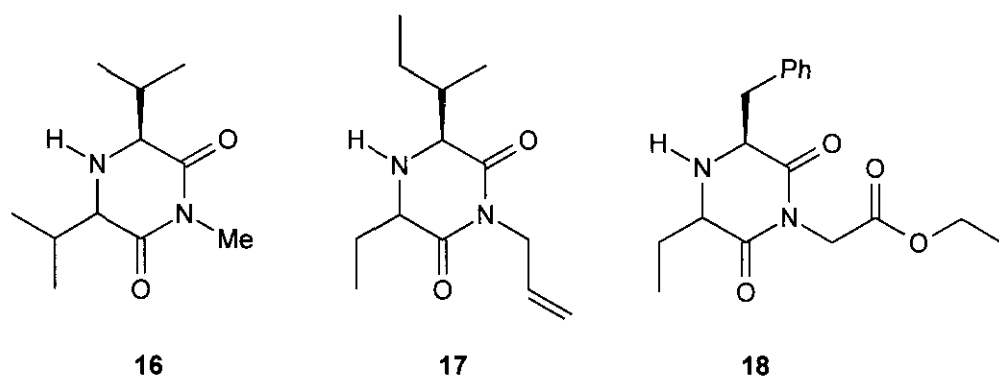


Figure 6: Some examples of 2,6-piperazinediones through cyclisation

EXPERIMENTAL

NMR spectra were recorded on Bruker spectrometers AM 360, AC 250 or AC 200 with TMS as internal standard. The chemical shifts are reported in ppm downfield from TMS. The attribution of the different carbons (C, CH, CH₂ or CH₃) were determined by ¹³C to ¹H polarisation transfer (DEPT). Elemental analyses were recorded by „Mikrochemisches Labor des Institutes für Organische Chemie und Biochemie der TU München“.

GC-MS were performed on a Varian MAT CH-5 apparatus coupled to a GC Carlo Erba 4160 column; chemical ionization (CI) and electronic ionization (EI; ionization potential of 70eV) were used. Medium pressure chromatography (0.9-2.0 bar) was conducted on silica gel (20-40 μm, Merck, Amicon) columns. All the commercial reagents were purchased from Aldrich, Merck and Fluka.

General procedure I a: 10 Mmol of α-amino acid in 100 mL of methanol are cooled to -30 °C. Then 10 mmol of ketone and isocyanide, each dissolved in 5 mL of methanol, are added. After 3 h the temperature is allowed to reach rt. When the reaction is completed (clear solution; 3 h -14 d) the solvent is removed *in vacuo*. Small amounts of the educts can be removed by washing an ethereal solution with water. The mixtures of diastereomers are viscous oils or sticky solids. The analytical data is only given for the main diastereomer. The 2,6-piperzinediones are separated from the 1,1'-iminodicabocyclic acid derivatives by flash chromatography.

General procedure I b: To 12 mmol of α-amino acid suspended in 100 mL of methanol, 10 mmol of ketone and 12 mmol of isocyanide, each dissolved in 5 mL of methanol, are added. When the reaction is

completed (2 d-5 d) the solvent is removed *in vacuo*. The educt excesses can be removed by washing the suspension of the residue in 50 mL of CH_2Cl_2 with water. The mixtures of diastereomers are viscous oils or sticky solids. The analytical data is only given for the main diastereomer. Diastereomers are separated by flash chromatography.

General procedure II: 10 Mmol of α -amino acid in 100 mL of methanol are cooled to -30°C . Then 10 mmol of aldehyde and isocyanide, each dissolved in 5 mL of methanol, are added. After 3 h the temperature is allowed to reach rt. When the reaction is completed (clear solution; 3 d–14 d) the solvent is removed *in vacuo*. The remaining oil is dissolved in 100 mL of THF, containing 15 mmol of potassium *tert.*-butoxide and is refluxed for 3 d. The solvent is removed *in vacuo*. The residue is solved in 50 mL of CH_2Cl_2 and washed three times with 20 mL of water. The 2,6-piperazinediones are separated from the 1,1'-iminodicarboxylic acid derivatives by flash chromatography.

***N*-(1-(*N*-Methylcarbamoyl) -L-methylethyl) -L-valine methyl ester (8)**

General procedure I a, with adding 40 mmol of acetone instead of 10 mmol of ketone. **Yield:** 2.16 g = 94 %; slightly yellow oil. $^1\text{H-NMR}$ (360 MHz, CDCl_3): δ = 0.94 (d, 3H, J = 6.6 Hz, $(\text{CH}_3)_2\text{-CH-}$); 0.96 (d, 3H, J = 6.6 Hz, $(\text{CH}_3)_2\text{-CH-}$); 1.22 (s, 3H, $(\text{CH}_3)_2\text{-C-}$); 1.27 (s, 3H, $(\text{CH}_3)_2\text{-C-}$); 1.85 (m, 1H, $(\text{CH}_3)_2\text{-CH-}$); 2.79 (d, 3H, J = 4.9 Hz, -CO-NH-CH_3); 3.00 (d, 1H, J = 5.8 Hz, $(\text{CH}_3)_2\text{-CH-CH-}$); 3.71 (s, 3H, -O-CH_3); 7.38 (br, 1H, -CO-NH-). $^{13}\text{C-NMR}$ (90.6 MHz, CDCl_3): δ = 18.4 ($(\text{CH}_3)_2\text{-CH-}$); 18.9 ($(\text{CH}_3)_2\text{-CH-}$); 23.1 ($(\text{CH}_3)_2\text{-C-}$); 25.7 (-CO-NH-CH_3); 27.6 ($(\text{CH}_3)_2\text{-C-}$); 32.4 ($(\text{CH}_3)_2\text{-CH-}$); 51.5 (-O-CH_3); 58.9 ($(\text{CH}_3)_2\text{-C-}$); 61.5 ($(\text{CH}_3)_2\text{-CH-CH-}$); 176.4 (-CO-NH-); 177.0 (-CO-O-CH_3). **GC-MS (EI, 70 eV):** m/z (%): 172 (100, $\text{M}^+ \text{-CO-NH-CH}_3$); 112 (93, $\text{M}^+ \text{-CO-NH-CH}_3/\text{-CO-O-CH}_3/\text{-H}$). **Anal.** Calcd for $\text{C}_{11}\text{H}_{22}\text{N}_2\text{O}$: C, 57.38; H, 9.63; N, 12.16. Found: C, 57.22; H, 9.43; N, 12.46.

***N*-(1-(*N*-Methylcarbamoyl) -L-phenylethyl) -L-valine methyl ester (9)**

General procedure I b. **Yield:** 1.86 g = 64 %; colourless oil. $^1\text{H-NMR}$ (360 MHz, CDCl_3): δ = 0.94 (d, 3H, J = 7.2 Hz, $(\text{CH}_3)_2\text{-CH-}$); 0.99 (d, 3H, J = 6.5 Hz, $(\text{CH}_3)_2\text{-CH-}$); 1.59 (s, 3H, $\text{CH}_3\text{-C-C}_6\text{H}_5$); 1.87 (m, 1H, $(\text{CH}_3)_2\text{-CH-}$); 2.39 (br, 1H, -NH-CH-); 2.80 (d, 3H, J = 4.5 Hz, -CO-NH-CH_3); 3.04 (d, 1H, J = 5.8 Hz, $(\text{CH}_3)_2\text{-CH-CH-}$); 3.56 (s, 3H, -O-CH_3); 7.24 (t, 1H, J = 7.1 Hz, C_6H_5); 7.30 (t, 2H, J = 7.1 Hz, C_6H_5); 7.41 (d, 2H, J = 7.8 Hz, C_6H_5). $^{13}\text{C-NMR}$ (90.6 MHz, CDCl_3): δ = 18.7 ($(\text{CH}_3)_2\text{-CH-}$); 19.0 ($(\text{CH}_3)_2\text{-CH-}$); 22.1 ($\text{CH}_3\text{-C-C}_6\text{H}_5$); 26.0 (-CO-NH-CH_3); 32.7 ($(\text{CH}_3)_2\text{-CH-}$); 51.5 (-O-CH_3); 61.7 ($(\text{CH}_3)_2\text{-CH-CH-}$); 65.0 ($\text{CH}_3\text{-C-C}_6\text{H}_5$); 125.6/127.2/128.3/143.7 (C_6H_5); 175.0 (-CO-NH-); 176.0 (-CO-O-CH_3). **GC-MS (EI, 70 eV):** m/z (%): 234 (100, $\text{M}^+ \text{-CO-NH-CH}_3$); 174 (56, $\text{M}^+ \text{-CO-NH-CH}_3/\text{-CO-O-CH}_3/\text{-H}$). **Anal.** Calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.57; H, 8.26; N,

9.39.

***N*-(1-(*N*-*tert*-Butylcarbamoyl)cyclohexyl)-*L*-valine methyl ester (10)**

General procedure I a. **Yield:** 2.12 g = 68 %; colourless, sticky solid. **¹H-NMR** (CDCl₃, 360 MHz): δ = 0.98 (d, 3H, ³J = 6.9 Hz, CH₃-CH-)/0.91 (d, 3H, ³J = 6.7 Hz, CH₃-CH-); 1.32 (s, 9H, (CH₃)₃-C-); 1.4–2.4 (br, 11H, (CH₃)₂-CH- and -CH₂-CH₂-); 2.99 (d, 1H, ³J = 5.8 Hz, -NH-CH-); 3.69 (s, 3H, -CH-CO-O-CH₃); 6.79 (br, 1H, -CO-NH-). **¹³C-NMR** (CDCl₃, 90.6 MHz): δ = 18.3/19.5 ((CH₃)₂-CH-); 21.9/22.2/25.4/31.5/36.5 (-CH₂-CH₂-); 28.6 ((CH₃)₃-C-); 33.3 ((CH₃)₂-CH-); 50.2 ((CH₃)₃-C-); 51.5 (-O-CH₃); 61.3 (-NH-CH-); 61.8 (-NH-C-CO-); 175.5 (-CO-NH-C-); 176.1 (-CO-O-CH₃). **GC-MS (EI, 70 eV):** m/z (%): 253 (3, M⁺-CO-O-CH₃); 212 (100, M⁺-CO-NH-C₄H₉); 152 (42, M⁺-CO-NH-C₄H₉-CO-O-CH₃/H). **IR (CHCl₃) [cm⁻¹]:** 3358; 2965 (st); 2934 (st); 2859; 1731 (st); 1665 (st); 1510 (st); 1453 (st); 1391; 1364; 1255; 1228; 1202; 1197; 1178; 1152. **Anal.** Calcd for C₁₇H₃₂N₂O₃: C, 65.35; H, 10.32; N, 8.97. Found: C, 64.87; H, 10.25; N, 9.28.

***N*-(1-((*N*-Ethyl-2-(methyloxycarbonyl))carbamoyl)cyclohexyl)-*L*-valine methyl ester (11)**

General procedure I a. **Yield:** 1.05 g = 64 %; 2.28 g = 98 %; colorless oil. **¹H-NMR** (CDCl₃, 200 MHz): δ = 0.96 (d, 3H, ³J = 6.9 Hz, CH₃-CH-)/0.91 (d, 3H, ³J = 6.8 Hz, CH₃-CH-); 2.4–1.3 (br, 11H, (CH₃)₂-CH- and -CH₂-CH₂-); 3.68 (s, 3H, -CH₂-CO-O-CH₃); 3.09 (d, 1H, ³J = 5.9 Hz, -NH-CH-); 3.74 (s, 3H, -CH-CO-O-CH₃); 3.97 (dd, 2H, ³J = 5.9/5.6 Hz, -NH-CH₂-CO-); 7.43 (t, 1H, ³J = 6.6 Hz, -CO-NH-). **¹³C-NMR** (CDCl₃, 62.9 MHz): δ = 17.6/18.5 ((CH₃)₂-CH-); 21.3/21.5/24.8/31.5/35.1 (-CH₂-CH₂-); 31.6 ((CH₃)₂-CH-); 40.4 (-NH-CH₂-); 50.8/51.4 (-O-CH₃); 60.4 (-NH-C-CO-); 60.8 (-NH-CH-); 169.8 (-CO-NH-CH₂-); 175.5/176.0 (-CO-O-CH₃). **GC-MS (EI, 70 eV):** m/z (%): 269 (4, M⁺-CO-O-CH₃); 212 (100, M⁺-CO-NH-CH₂-CO-O-CH₃); 152 (62, M⁺-CO-O-CH₃/CO-NH-CH₂-CO-O-CH₃). **Anal.** calcd for C₁₆H₂₈N₂O₅: C, 58.52; H, 7.84; N, 8.53. Found: C, 58.68; H, 8.05; N, 8.34.

1-*N*-Methyl-5-(*S*)-methyl-2,6-piperazinedione-3-spirocyclohexane (12)

General procedure I a with the addition of one equivalent triethylamine; purification by chromatography (hexane : ethyl acetate 4 : 1). **Yield:** 0.9 g = 43 %; white crystals. **mp:** 67° C. **¹H-NMR** (CDCl₃, 360 MHz): δ = 1.41 (d, 3H, ³J = 6.8 Hz, -CH-CH₃); 1.45–2.1 (br, 10H, -CH₂-); 3.03 (s, 3H, -C-CH₃); 3.66 (q, 1H, ³J = 6.8 Hz, -NH-CH-). **¹³C-NMR** (CDCl₃, 90.6 MHz): δ = 17.4 (-CH-CH₃); 20.0/20.3/26.1/29.6/34.1 (-CH₂-); 25.2 (-N-CH₃); 49.0 (-NH-CH-); 57.9 (-CH₂-C-CH₂-); 173.9 (-N-CO-); 176.7 (-CH-CO-). **GC-MS (EI, 70 eV):** m/z (%): 210 (34, M⁺); 125 (100); 182 (8); 167 (12). **IR (Film) [cm⁻¹]:** 3311; 2932 (st); 2857; 1721 (st); 1675 (st); 1451; 1418; 1356; 1284 (st); 1885; 1143; 1057; 1028. **Anal.** Calcd for C₁₁H₁₈N₂O₂: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.69; H, 8.60; N, 13.52.

1-*N*-Methoxyacetyl-5-(*S*)-isopropyl-2,6-piperazinedione-3-spirocyclohexane (13)

General procedure I a with the addition of one equivalent triethylamine; purification by chromatography (hexane : ethyl acetate 4 : 1. **Yield:** 2.1 g = 70 %; white crystals. **mp:** 58° C. **¹H-NMR** (CDCl₃, 360 MHz): δ = 0.92 (d, 3H, ³J = 6.9 Hz, -CH-(CH₃)₂)/1.12 (d, 3H, ³J = 6.8 Hz, -CH-(CH₃)₂); 1.3 – 2.2 (br, 10H, -CH₂-); 2.55 – 2.61 (m, 1H, ³J = 3.3/6.9 Hz, -CH-(CH₃)₂); 3.54 (d, 1H, ³J = 3.3 Hz, -NH-CH-); 3.71 (s, 3H, -O-CH₃); 4.46 (s, 2H, -CH₂-CO-). **¹³C-NMR** (CDCl₃, 90.6 MHz): δ = 16.8/19.9 (-CH-(CH₃)₂); 19.0/20.5/24.9/28.6/33.5 (-CH₂-); 28.4 (-NH-CH-CH-); 39.9 (-N-CH₂-); 51.8 (-O-CH₃); 57.2 (-CH₂-C-CH₂-); 57.8 (-NH-CH-); 168.1 (-CH-CO-N-CO-); 172.6 (-CH-CO-N-); 175.9 (-CH₂-CO-). **GC-MS (EI, 70 eV):** m/z (%): 296 (18, M⁺); 253 (100, M⁺ - C₃H₇); 226 (12); 152 (78); 167 (12). **IR (Film)** [cm⁻¹]: 3321 (w); 2933 (st.); 2857; 1755 (st.); 1729; 1683 (st.); 1440; 1403; 1370; 1323; 1210 (st.); 1186. **Anal.** Calcd for C₁₅H₂₄N₂O₄: C, 60.79; H, 8.16; N, 9.45. Found: C, 61.01; H, 7.93; N, 9.40.

1-*N*-Methyl-5-(*S*)-methyl-2,6-piperazinedione-3-spiro-1'-cyclohexane-4'-spiro-1''-2'',5''-dioxacyclopentane (14)

General procedure I a with the addition of one equivalent triethylamine; purification by chromatography (hexane : ethyl acetate 4 : 1. **Yield:** 1.80 g = 67 %; white crystals. **mp:** 105° C. **¹H-NMR** (CDCl₃, 360 MHz): δ = 1.45 (d, 3H, ³J = 6.8 Hz, -CH-CH₃); 1.5 – 2.5 (br, 8H, -C-CH₂-); 3.11 (s, 3H, -N-CH₃); 3.65 (q, 1H, ³J = 4.0 Hz, -NH-CH-); 3.96 (br, 4H, -O-CH₂-CH₂-O-). **¹³C-NMR** (CDCl₃, 90.6 MHz): δ = 17.4 (-CH-CH₃); 26.3 (-N-CH₃); 27.8/29.2/29.5/32.3 (-C-CH₂-); 49.4 (-NH-CH-); 57.2 (-NH-C-); 64.2/643 (-O-CH₂-CH₂-O-); 107.7 (-C-O-CH₂-); 174.1/176.4 (-CO-). **GC-MS (EI, 70 eV):** m/z (%): 268 (5, M⁺); 183 (15); 101 (100). **IR (KBr)** [cm⁻¹]: 3312; 2954; 2929; 2883; 1720; 1665 (st.); 1417; 1371; 1315; 1295; 1282; 1110 (st.). **Anal.** Calcd for C₁₃H₂₀N₂O₄: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.30; H, 7.33; N, 10.33.

1-*N*-Methyl-5-(*S*)-methyl-2,6-piperazinedione-3-spiro-1'-cyclohexane-4'-spiro-3''-(1''-*N*'-(methyl)-5''-(*S*)-methyl-2'',6''-piperazinedione) (15)

General procedure I a with 20 mmol of alanine, 20 mmol of methyl isocyanid and 2 g triethylamine; purification by chromatography (hexane : ethyl acetate 1 : 1), R_f: 0.65. **Yield:** 1.51 g = 45 %; violet crystals. **mp:** 109° C. **¹H-NMR** (CDCl₃, 360 MHz): δ = 1.46 (d, 6H, ³J = 6.8 Hz, -CH-CH₃); 1.42 – 1.61 (br, 2H, -CH₂-); 1.90 – 1.98 (br, 2H, -CH₂-); 2.12 – 2.22 (br, 2H, -CH₂-); 2.31 – 2.41 (br, 2H, -CH₂-); 3.13 (s, 6H, -N-CH₃); 3.75 (q, 2H, ³J = 6.8 Hz, -NH-CH-). **¹³C-NMR** (CDCl₃, 90.6 MHz): δ = 17.8 (-CH-CH₃); 26.4 (-N-CH₃); 27.2/30.0 (-CH₂-); 49.5 (-NH-C-); 56.7 (-NH-CH-); 173.9/176.6 (-CO-). **¹H-¹H-TOCSY** (CDCl₃, 250 MHz): δ = 3.75 with 1.46; 2.31 – 2.41 with 2.12 – 2.22/1.90 – 1.98/1.42 – 1.61; 2.12 – 2.22 with 2.31 – 2.41/1.90 – 1.98/1.42 – 1.61; 1.90 – 1.98 with 2.31 – 2.41/2.12 – 2.22/1.61 –

1.42; 1.42 – 1.61 with 2.31 – 2.41/2.12 – 2.22/1.90 – 1.98. **¹H-¹³C-correlation** (CDCl₃, 250 MHz): δ = 56.7 with 3.75; 30.0 with 2.12 – 2.22/1.421 – 161; 27.2 with 2.31 – 2.41/1.90 – 1.98; 26.4 with 3.13; 17.8 with 1.46. **GC-MS (EI, 70 eV)**: *m/z* (%) 336 (8, M⁺); 251 (28); 169 (55); 154 (49); 97 (100). **IR (KBr)** [cm⁻¹]: 3312; 2954; 2929; 2883; 1720; 1665; 1417; 1371; 1315; 1295; 1282; 1110. **Anal.** Calcd for C₁₆H₂₄N₄O₄: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.38; H, 7.23; N, 16.27.

1-*N*-Methyl-3, 5-diisopropyl-2,6-piperazinedione (16)

General procedure II; purification by chromatography (hexane : ethyl acetate 4 : 1). **Yield**: 1.5 g = 71 %; white, sticky solid. **¹H-NMR** (CDCl₃, 360 MHz): δ = 0.93 (d, 6H, ³J = 7.1 Hz, –CH–CH₃); 1.10 (d, 6H, ³J = 7.1 Hz, –CH–CH₃); 2.58 (m, 2H, J = 2.6 Hz/7.1 Hz, –CH–(CH₃)₂); 3.36 (s, 3H, –N–CH₃). **¹³C-NMR** (CDCl₃, 90.6 MHz): δ = 16.4/19.2 (–CH–CH₃); 25.8 (–N–CH₃); 29.0 (–NH–CH–CH); 63.7 (–NH–CH–); 172.9 (–N–CO–). **GC-MS (EI, 70 eV)**: *m/z* (%): 212 (8, M⁺); 169 (100); 127 (51); 112 (26). **Anal.** Calcd for C₁₁H₂₀N₂O₂: C, 62.24; H, 9.50; N, 13.20. Found: C, 61.86; H, 9.78; N, 13.54.

1-*N*-Allyl-3-(*S*)-(2)-butyl-5-ethyl-2,6-piperazinedione (17)

General procedure II; purification by chromatography (hexane : ethyl acetate 4 : 1). **Yield**: 1.72 g = 72 %; white, sticky solid. **¹H-NMR** (CDCl₃, 360 MHz): δ = 0.8 – 1.2 (m, 9H, –CO–CH–CH₂–CH₃/–CH–CH–CH₂–CH₃); 1.20 – 2.40 (m, 3H, –CO–CH–CH₂–CH₃ and –CH–CH–CH₂–CH₃); 3.15 – 3.65 (m, 2H, –CH–NH–CH–); 4.25 – 4.45 (m, 2H, CH₂=CH–CH₂–); 5.10 – 5.22 (m, 2H, CH₂=CH–CH₂–); 5.70 – 5.90 (m, 1H, CH₂=CH–CH₂–). **¹³C-NMR** (CDCl₃, 90.6 MHz): δ = 9.9 (–CO–CH–CH₂–CH₃); 16.0 (–CH–CH–CH₃); 24.1 (–CH–CH–CH₃); 26.0 (–CH–CH–CH₂–CH₃); 35.3 (–CO–CH–CH₂–); 41.2 (CH₂=CH–CH₂–); 60.0/62.5 (–CH–NH–CH); 117.2 (CH₂=CH–CH₂–); 132.1 (CH₂=CH–CH₂–); 172.6/172.9 (–CO–N–CO–). **GC-MS (EI, 70 eV)**: *m/z* (%): 238 (8, M⁺); 181 (63); 153 (25); 126 (35); 98 (66); 41 (100). **Anal.** Calcd for C₁₃H₂₂N₂O₂: C, 65.52; H, 9.30; N, 11.75. Found: C, 65.84; H, 9.03; N, 12.06.

1-*N*-Ethoxyacetyl-3-(*S*)-benzyl-5-ethyl-2,6-piperazinedione (18)

General procedure II; purification by chromatography (hexane : ethyl acetate 4 : 1). **Yield**: 2.2 g = 68 %; white, sticky solid. **¹H-NMR** (CDCl₃, 360 MHz): δ = 0.92 (t, 3H, ³J = 7.5 Hz, –CH–CH₂–CH₃); 1.22 – 1.30 (m, 3H, ³J = 3.5 Hz, –O–CH₂–CH₃); 1.60 – 2.00 (m, 2H, –CH–CH₂–CH₃); 3.01 (d, 1H, J = 8.4 Hz, –CH–CH₂–Ar); 3.44 (d, 1H, J = 3.8 Hz, –CH–CH₂–Ar); 3.47 (dd, 1H, J = 3.5 Hz, –CH–CH₂–Ar); 3.78 (dd, 1H, J = 3.5 Hz, –CH–CH₂–CH₃); 4.19 (q, 2H, J = 7.1 Hz, –O–CH₂–CH₃); 4.49 (d, 2H, J = 3.1 Hz, –N–CH₂–); 7.10 – 7.40 (m, 5H, Ar). **¹³C-NMR** (CDCl₃, 90.6 MHz): δ = 9.6 (–CH–CH₂–CH₃); 14.0 (–O–CH₂–CH₃); 24.0 (–CH–CH₂–CH₃); 36.6 (–CH₂–Ar); 40.5 (–N–CH₂–CO–); 55.7 (–CH–CH₂–CH₃); 59.9 (–CH–CH₂–Ar); 61.4 (–O–CH₂–); 127.0/128.7/128.8 (Ar); 136.6 (–CH₂–C_{Ar}–); 167.6/175.0/172.7 (–CO–).

GC-MS (EI, 70 eV): m/z (%): 318 (3, M^+); 245 (7); 227 (100); 199 (5); 181 (24); 153 (28). **Anal.** Calcd for $C_{17}H_{22}N_2O_4$: C, 64.12; H, 6.97; N, 8.80. Found: C, 63.94; H, 7.41; N, 8.39.

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 13. Crystallographic data for $C_{13}H_{20}N_2O_4$ **14**: $M_r = 268.31$, monoclinic, $P2_1$ (I.T.-Nr.: 4), $a = 782.7(1)$, $b = 801.6(1)$, $c = 1097.7(1)$ pm, $\beta = 93.80(1)^\circ$, $V = 687.2(1) \cdot 10^6$ pm³; $Z = 2$; $\rho_{calcd} = 1.297$ gcm⁻³, $F_{000} = 288$, $\mu = 1.0$ cm⁻¹. 4307 data were collected at 294 K on a NONIUS MACH3 diffractometer with graphite monochromator, $\lambda(Mo-K\alpha) = 0.71073$ Å. 64 data were rejected (10 systematically absent, 54 negative intensities). After merging ($R_{int} = 0.020$) all 2734 unique data ($I > 0.0$) were used in refinements. The structure was solved with direct methods, and refined by full-matrix least-squares calculations, with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were found and refined. Refinement was concluded with $R1 = 0.034$ and $wR2 = 0.092$. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-407655, the names of the authors and the journal citation, or from the author E.H.

Received, 1st August, 1997