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Ugi Reactions with trifunctional α-Amino Acids, Aldehydes, Isocyanides and Alcohols.

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Dedicated to Prof. Dr. Hans Fritz on the occasion of his 60th birthday

Abstract : 1,1'-iminodicarboxylic acid derivatives, which are similar to many natural substances can be synthesized in excellent yields and with high stereoselectivity by a one-pot reaction of α-amino acids, aldehydes, isocyanides and alcohols. Copyright © 1996 Elsevier Science Ltd

Chemical compounds are usually synthesized in several reaction steps. The intermediates must be separated and purified before they can be used as an educt of the next reaction. The total yield of such an iterative synthesis sharply decreases with the number of steps.

One-pot multicomponent reactions (MCR)[1] are now widely used to prepare many compounds quickly and with high yields. A very effective variation of the well-known Ugi reaction (U-4CR)[2] is the recently published five-center-four-component reaction (U-5C-4CR)[3]. It combines very high yields (usually more than 95 %) and excellent stereoselectivity (d.e. ≈ 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[4]. Opines[5], 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[6].

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[7,8] of the U-5C-4CR is given in **Fig. 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** 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.

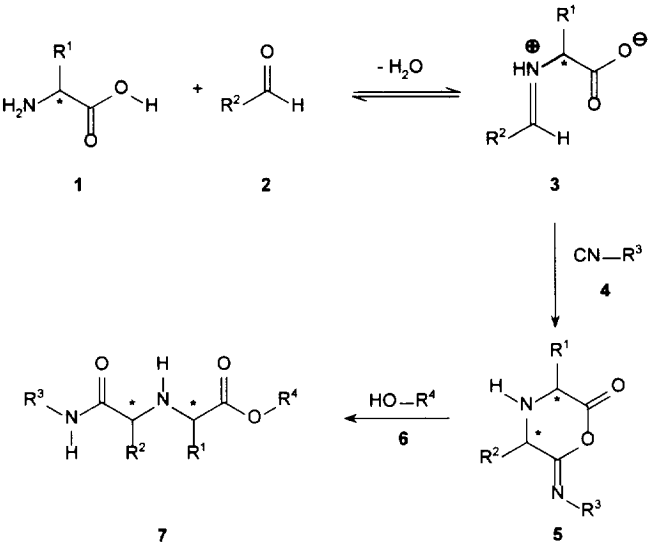

Figure 1: Postulated reaction mechanism of the U-5C-4CR.

With most of the trifunctional α-amino acids (L-serine, L-threonine, L-tyrosine, L-asparagine, L-glutamine, L-methionine) the functional group of the side chain does not participate in the Ugi reaction. No by-products are observed with amino acids with hydroxy groups as a third functional group. For both L-serine **8** und L-tyrosine **9**the U-5C-4CR proceed with the usual high yields (98% in both cases). Also, no side reactions are observed for L-tryptophan **10** (see **Fig. 2**).

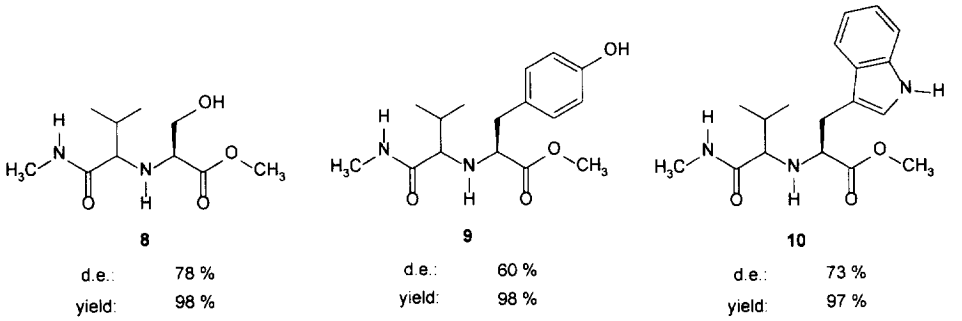

Figure 2: Examples of products of trifunctional α-amino acids in the U-5C-4CR.

L-Lysine, L-glutamic acid and L-aspartic acid are exceptions: the functional groups in their side chains either participate in parallel MCRs or react as a nucleophile instead of the solvent alcohol.
In the case of L-lysine a ε-lactam can be isolated instead of the corresponding methyl ester. This ε-lactam **11** is either formed from the postulated intermediate O-acylamide by nucleophilic attack of the amino function of the side chain and a subsequent rearrangement or by a nucleophilic substitution of the ester which is formed by the U-5C-4CR by the ε-amino function.

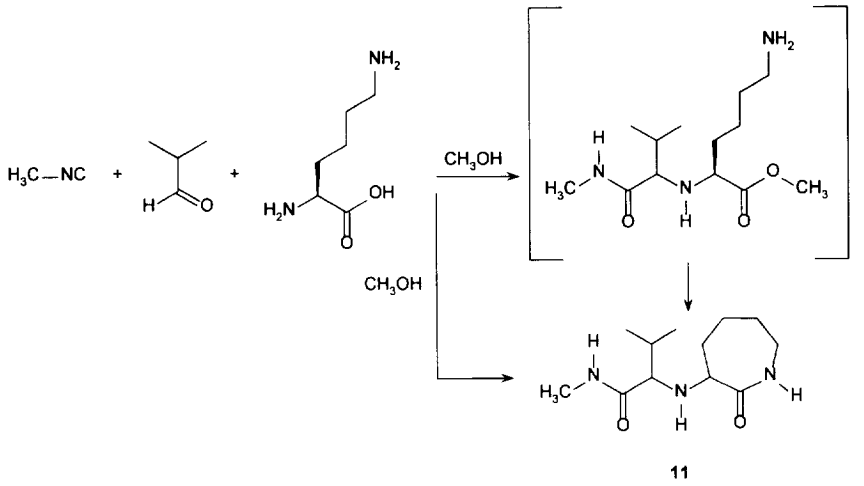

Figure 3: The formation of ε-lactams from L-lysine.

L-Ornithine has one methylene group less in its side chain than L-lysine. Probably due to steric reasons the responding ε-lactam is only formed in traces. The main product is the U-5C-4CR-product with a free amino function in the side chain. Due to the nearly quantitative yields subsequent one-pot reactions are possible. L-Histidine reacts like the other α-amino acids to the aforementioned U-5C-4CR products.

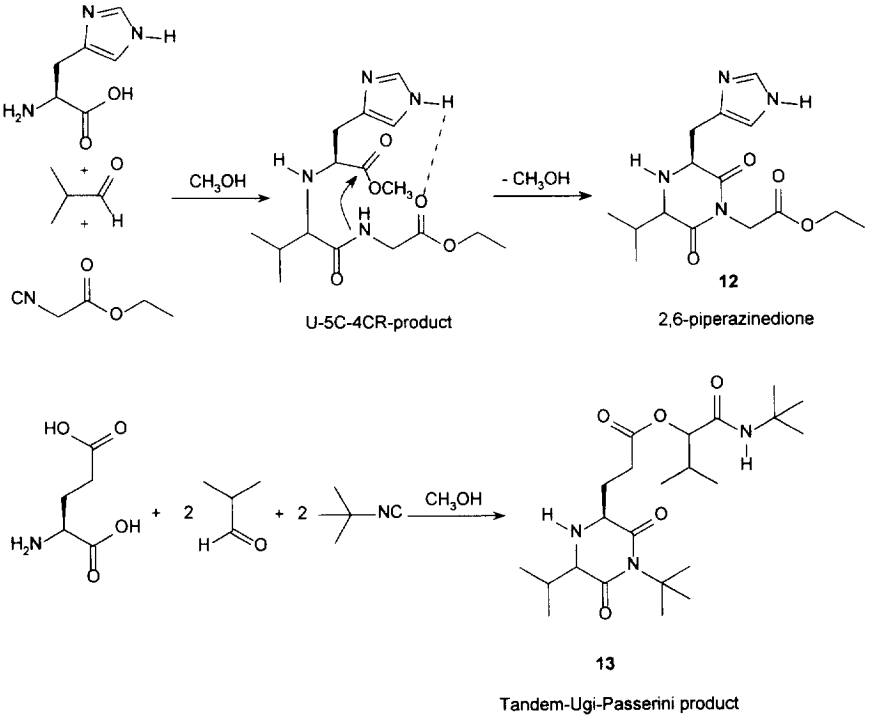

Figure 4: L-Histidine and L-glutamic acid in the Ugi-reaction.

In the case of the use of isocyano acetic acid ethyl ester, however, the reaction leads to 2,6-piperazinediones. The methoxy group of the U-5C-4CR ester is substituted by the amid nitrogen of the former isocyanide. The required proximity is assumed to be achieved by hydrogen bonds (see **Fig. 4**).
Tandem-Ugi-Passerini products are also formed from L-aspartic acid **14**. No 2,6-piperazinediones are observed (see **Fig. 5**). The high selectivity of these combined reactions is exceptional since only the carboxy group of the side chain reacts in the Passerini reaction.

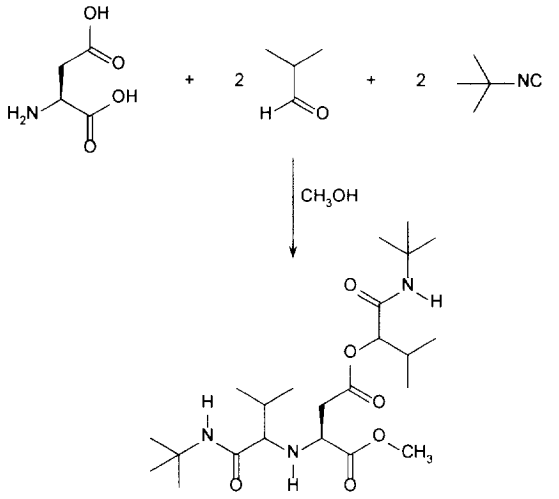

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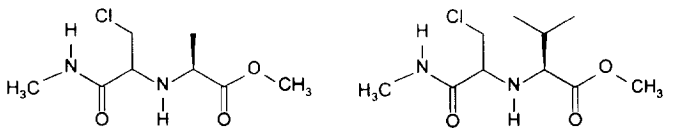
Figure 5: The Tandem-Ugi-Passerini reaction with L-aspartic acid.

Difunctional, halogen substituted aldehydes were also investigated. The reaction of chloroactaldehyde with methylisocyanide in methanol was investigated for several amino acids. Side reactions, e.g. the substitution of the chloro group by the secondary amine of the U-5C-4CR product, were seldom (up to 10%). The diasteromeric excesses and the yields were less (yield:~40 %; d.e.:~35 %) than those usually observed in the the U-5C-4CR reactions. This is probably due to the reduced reactivity of the aldehyde resulting from the α-halogen substituent. It should be possible to achieve higher yields by choosing appropriate reaction conditions. The products **15** und **16** of the reaction with L-alanine and L-valine are given in **Fig. 6**.



15 **16**

d.e. : 20 % d.e. : 54 %
yield : 40 % yield : 40 %

Figure 6 : Chloro-substituted U-5C-4CR products.

Recent investigations[9] have shown that the diastereomeric excess can be controlled by temperature and metal catalysts. It was also shown[10], that other classes of such as amines and thiols can react as nucleophiles in the U-5C-4CR. Like other multicomponent reactions, the U-5C-4CR is well suited for generating combinatorial chemical libraries[11,12,13]. Several libraries have been synthesized and are being tested for pharmaceutically active compounds.

These results confirm the authors' opinion that multicomponent reactions in general, and the U-4CR in particular, will play a prominent part in research, development and in technical applications.

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, CH_2 or CH_3) were determined by ^{13}C to ^{1}H 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: 10 mmol α-amino acid in 100 ml methanol are cooled to -30 °C. Then 10 mmol aldehyde and isocyanide, each dissolved in 5 ml methanol, are added. After 3h the temperature is allowed to reach room temperature. When the reaction is completed (clear solution; 3h – 2d) the solvent is removed *in vacuo*. The crude product is virtually free of by-products and often needs no further purification. Small amounts of the educts can be removed by washing an etherial solution with water. The mixtures of diastereomers are viscous oils or sticky solids. The diastereomers are separated by flash chromatography. The analytical data is only given for the main diastereomer.

N-(1-(N-Methylcarbamoyl)-2-methylpropyl)-L-serine methyl ester (8)

General procedure with the addition of one equivalent triethylamine.

Yield: 2.28 g = 98 %; white , sticky solid. Diastereomeric excess: 78 %

^{1}H-NMR (250 MHz, $CDCl_3$,): δ = 0.96 (d, 3H, $\underline{CH_3}$–CH–, J = 6.9 Hz)/1.00(d, 3H, $\underline{CH_3}$–CH–, J = 6.9 Hz); 2.12 (m, 1H, $(CH_3)_2$–$\underline{CH}$–CH–, J = 4.8 Hz); 2.81 (d, 3H, –CO–NH–$\underline{CH_3}$, J = 4.9 Hz); 2.98 (d, 1H, –NH–$\underline{CH}$–CO–NH–, J = 4.7 Hz); 3.31 (t, 1H, –$\underline{CH}$–CH_2–, J = 4.3 Hz); 3.79 (d, 2H, –$\underline{CH_2}$–, J = 4.4 Hz); 3.71 (s, 3H, –O–$\underline{CH_3}$); 7.23 (br., 1H, –CO–$\underline{NH}$–).

^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 19.6/17.7 ($\underline{C}H_3$–CH–); 25.8 (–CO–NH–$\underline{C}H_3$); 31.4 ($(CH_3)_2$–$\underline{C}$H–); 52.3 (–O–$\underline{C}H_3$); 61.5 (–$\underline{C}$H–CH_2–); 62.1 (–$\underline{C}H_2$–); 66.9 (–NH–$\underline{C}$H–CH–); 173.2 (–$\underline{C}$O–NH–CH_3); 174.4 (–$\underline{C}$O–O–CH_3).

GC-MS (EI, 70 eV): m/e (%): 174 (100, M^+- CO–NH–CH_3); 127 (11); 114 (58, M^+- CO–NH–CH_3/ - CO–O–CH_3/- H); 102 (67); 96 (11); 86 (12).

Microanalysis: calcd for $C_{10}H_{20}N_2O_4$ (232.28) C: 51.71; H: 8.68; N: 12.06; found C: 51.44; H: 8.93; N: 11.81.

N-(1-(N-Methylcarbamoyl)-2-methylpropyl)-L-thyrosine methyl ester (9)

General procedure with the addition of one equivalent triethylamine.

Yield: 3.21 g = 98 %; white , sticky solid. Diastereomeric excess: 60 %

^{1}H-NMR (250 MHz, $CDCl_3$) δ = 0.64 (d, 3H, $\underline{CH_3}$–CH–, J = 6.9 Hz)/0.65 (d, 3H, $\underline{CH_3}$–CH–, J = 7.0 Hz); 2.13 (m, 1H, $(CH_3)_2$–$\underline{CH}$–CH–, J = 4.0 Hz); 2.81 (d, 3H, –CO–NH–$\underline{CH_3}$, J = 4.9 Hz); 2.87 (d, 1H,

–NH–CH–CO–NH–, J = 3.8 Hz); 2.89 – 3.05 (m, 3H, –CH–CH_2–); 3.67 (s, 3H, –O–CH_3); 6.81 (d, 2H, –CH_2–C=CH–, J = 8.4 Hz); 7.02 (d, 2H, –CH=C–OH, J = 8.3 Hz); 7.65 (br., 1H, –CO–NH–).
^{13}C-NMR (62.9 MHz, $CDCl_3$) δ = 16.9/19.2 (CH_3–CH–); 25.9 (–CO–NH–CH_3); 31.0 ((CH_3)$_2$–CH–); 38.1 (–CH_2–); 52.0 (–O–CH_3); 63.5 (–CH–CH_2–); 67.4 (–NH–CH–CH–); 115.9 (–CH_2–C=CH–); 127.1 (=C–OH); 130.2 (–CH=C–OH); 156.3 (–CH_2–C–); 174.5/174.9 (–CO–O–CH_3)/(–CO–NH–CH_3).
GC-MS (EI, 70 eV): m/e (%): 250 (52, M^+- CO–NH–CH_3); 201 (15, M^+- CH_2–C_6H_4–OH); 190 (23, M^+- CO–NH–CH_3/- CO–O–CH_3/- H); 179 (12, HO–C_6H_4–CH_2–CH–$COOCH_3$); 147 (8); 137 (16); 107 (21, CH_2–C_6H_4–OH); 72 (100).
Microanalysis: calcd for $C_{16}H_{24}N_2O_4$ (308.38) C: 62.32; H: 7.84; N: 9.08; found C: 61.94; H: 8.07; N: 9.14.

N-(1-(N-Methylcarbamoyl)-2-methylpropyl)-L-tryptophane methyl ester (10)

General procedure with the addition of one equivalent triethylamine.
Yield: 3.21 g = 97 %; yellow , sticky solid. Diastereomeric excess: 73 %
^{1}H-NMR (360 MHz, $CDCl_3$): δ = 0.50 (d, 3H, CH_3–CH–, J = 7.0 Hz)/0.60 (d, 3H, CH_3–CH–, J = 6.9 Hz); 1.91 (d, 2H, –CH_2–, J = 4.9 Hz); 1.95 – 2.15 (m, 1H, (CH_3)$_2$–CH–CH–); 2.78 (d, 3H, –NH–CH_3, J = 4.9 Hz); 2.84 (d, 1H, –NH–CH–CO–NH–, J = 3.5 Hz); 2.86 (d, 1H,–NH–CH–CO–O–, J = 5.9 Hz); 3.68 (s, 3H, –O–CH_3); 6.8 – 7.8 (m, 5H, Arom., –NH–CH–C–); 8.38 (br., 1H, –CO–NH–).
^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 16.9/19.9 (CH_3–CH–); 25.7 (–CO–NH–CH_3); 28.7 (–CH_2–); 30.9 ((CH_3)$_2$–CH–); 52.0 (–O–CH_3); 62.4/67.7 (–NH–CH–); 110.2 (–CH_2–C=CH–); 111.4/118.5/119.7/ 122.5/122.9/126.5/137.3 (Arom., –NH–CH–C–); 174.8 (–CO–OCH_3); 173.5 (–CO–NH–CH_3).
GC-MS (EI, 70eV): m/e (%): 273 (21, M^+- CO–NH–CH_3); 272 (2, M^+- CO–O–CH_3); 213 (2, M^+- CO–NH–CH_3/- CO–O–CH_3/- H); 201 (28); 160 (11); 142 (10); 130 (100); 72 (85).
Microanalysis: calcd for $C_{18}H_{25}N_3O_3$ (331.41) C: 65.24; H: 7.60; N:12.68; found C: 65.01; H: 7.14; N: 12.99.

N-(1-(N-Methylcarbamoyl))-2-methylpropyl)-L-lysine-ε-lactam (11)

10 mmol isobutyric aldehyde (0.72 g) and 10 mmol methylisocyanide (0.41 g), each in 10 ml methanol, are added to a stirred suspension of 10 mmol L-lysinhydrochloride (1.83 g) and 10 mmol NaOH (0.40 g). After 7 days the reaction is completed and the solvent is removed in vacuo. The residue is dissolved in rther and washed three times with H_2O. The organic phase is dried over $MgSO_4$ and the solvent is removed.
Yield: 1.53 g = 62 %; white, sticky solid. Diastereomeric excess: 60 %
^{1}H-NMR (360 MHz, $CDCl_3$): δ = 0.90 (d, 3H, (CH_3)$_2$–CH–, J = 6.8 Hz)/0.99 (d, 3H, (CH_3)$_2$–CH–, J = 6.9 Hz); 1.3 – 2,05 (br., 6H, –CH–CH_2–CH_2–CH_2–); 2.05 – 2.15 (m, 1H,–CH–(CH_3)$_2$, J = 4.8 Hz); 2.79 (d, 3H, –CO–NH–CH_3, J = 4.8 Hz); 3.05 (d, 1H, –NH–CH–CH–, J = 4.7 Hz); 3.1 – 3.4 (m, 3H, –NH–CH–CH_2–/ –NH–CH_2–); 7.16 (t, 1H, –CO–NH–CH_2–, J = 6.1 Hz); 7.46 (1H, –CO–NH–CH_3).
^{13}C-NMR (90,6 MHz, $CDCl_3$): δ = 17.6/19.5 ((CH_3)$_2$–CH–); 25.5 (–NH–CH_3); 27.9/28.5/30.9 (–CH–CH_2–CH_2–CH_2–); 31.9 ((CH_3)$_2$–CH–); 41.6 (–NH–CH_2–); 58.7/65.6 (–CH–NH–CH–); 174.6 (–CO–NH–CH_3); 178.2 (–CO–NH–CH_2–).
GC-MS (EI, 70eV): m/e (%): 241 (12, M^+); 210 (3); 198 (14, M^+- C_3H_7); 183 (100, M^+- CO–NH–CH_3).
Microanalysis: calcd for $C_{12}H_{23}N_3O_2$ (241.33) C: 59.72; H: 9.61; N: 17.41; found C: 59.22; H: 9.84; N: 17.42.

2,6-Piperazinedione (12)

Yield: 2.60 = 80 %; white, sticky solid. Diastereomeric excess: 44 %
^{1}H-NMR (360 MHz, $CDCl_3$): δ = 0.93 (d, 3H, J = 6.7 Hz, –CH–(CH_3)$_2$)/0.91 (d, 3H, –CH–(CH_3)$_2$, J = 6.8 Hz); 1.24 (t, 3H, –CH_2–CH_3, J = 7.1 Hz,); 1.90 (m, 1H, –CH–(CH_3)$_2$); 3.22 (m, 2H, –CH–CH_2–); 3.26 (m, 1H, –NH–CH–CH–); 3.74 (m, 1H, –CH–CH_2–); 4.03 (s, 2H,–CH_2–CO–); 4.25 (q, 2H, –O–CH_2–, J = 7.1 Hz); 7.25 (s, 1H, –CH_2–C=CH–N–); 8.30 (s, 1H, –N–CH–NH–); 8.80 (s, 1H, –NH–CH=N–).
^{13}C-NMR (90.6 MHz, $CDCl_3$) δ = 13.4 (–CH_2–CH_3); 18.6/19.4 ((CH_3)$_2$–CH–); 26.9 (–CH–CH_2–CH–); 31.4 (CH_3)$_2$–CH–); 41.0 (–CH_2–CO–); 58.8 (–NH–CH–CH_2–); 61.2 (–O–CH_2–); 65.7 (–NH–CH–CH–); 116.9 (–CH_2–C=CH–N–); 130.2 (–CH_2–C=CH–N–); 132.4 (–NH–CH=N–); 169.7/172.9/175.9 (–CO–).
GC-MS (EI, 70eV): m/z (%): 322 (2, M^+); 82 (100).

Microanalysis: calcd for $C_{15}H_{22}N_4O_4$ (322.36) C: 55.89; H: 6.88; N: 17.38; found C: 55.80; H: 7.17; N: 17.22.

2,6-Piperazinedione (13)

General procedure with 20 mmol of aldehyde and isocyanide.
Yield: 3.56 = 81 %; white, sticky solid.
^{1}H-NMR (360 MHz, $CDCl_3$): δ = 0.88 – 0.98 (m, 12H, $\underline{CH_3}$–CH–); 1.35 (s, 9H, $(\underline{CH_3})_3$C–); 1.39 (s, 9H, $(\underline{CH_3})_3$C–); 1.99 (m, 1H, $(CH_3)_2$–$\underline{CH}$–CH–NH–); 2.0/2.30 (m, 2H, –O–CO–$\underline{CH_2}$–CH_2–); 2.45 (m, 1H, –O–CH–$\underline{CH}$–$(CH_3)_2$); 2,40/2.68 (m, 2H, –O–CO–CH_2–$\underline{CH_2}$–); 4.25 (d, 1H, –NH–$\underline{CH}$–CH–, J = 11.2 Hz); 4.48 (dd, 1H, –NH–$\underline{CH}$–CH_2–, J = 4.3/8.8 Hz); 5.06 (d, 1H, –CO–$\underline{CH}$–O–, J = 3.3 Hz); 6.85 (s, 1H, –CH–$\underline{NH}$–CH–); 7.02 (s, 1H, –CO–$\underline{NH}$–).
^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 16.2/19.0/19.1/19.5 (–CH–$(\underline{CH_3})_2$); 24.0 (–NH–CH–$\underline{CH_2}$–CH_2–); 28.6/28.7 ($(\underline{CH_3})_3$C–); 29.3 (–NH–CH–$\underline{CH}$–); 29.7 (–NH–CH–CH_2–$\underline{CH_2}$–); 30.5 (–O–CH–$\underline{CH}$–); 51.5/51.6 (–$\underline{CH}(CH_3)_3$); 59.2 (–NH–$\underline{CH}$–CH_2–CH_2–); 64.5 (–NH–$\underline{CH}$–CH–); 78.4 (–O–CH–$\underline{CH}$–); 168.1/168.3 (–$\underline{CO}$–N–$\underline{CO}$–); 176.1/172.8 (–$\underline{CO}$–NH–/–$\underline{CO}$–O–).
GC-MS (EI, 70eV): m/z (%): 458 (0.5) [M^+], 357 (100).
Microanalysis: calcd for $C_{23}H_{41}N_3O_5$ (439.59) C: 62.84; H: 9.40; N: 9.56; found C: 62.59; H: 9.62; N: 9.09.

Tandem-Ugi-Passerini product (14)

General procedure with 20 mmol of aldehyde and isocyanide.
Yield: 3.88 = 85 %; white, sticky solid. Diastereomeric ratio: 5.0/2.7/1.3/1.0.
^{1}H-NMR (360 MHz, $CDCl_3$): δ = 0.8 – 1.08 (m, 12H, $\underline{CH_3}$–CH–); 1.36 (s, 9H, $(\underline{CH_3})_3$C–); 1.39 (s, 9H, $(\underline{CH_3})_3$C–); 2.09 (m, 1H, $(CH_3)_2$–$\underline{CH}$–CH); 2.32 (m, 1H, $(CH_3)_2\underline{CH}$–CH); 2.81 (m, 1H, CH–$\underline{CH_2}$–); 2.88 (m, 1H, –CO-$\underline{CH}$-NH-); 3.58 (m, 1H, –$\underline{CH}$–CH_2–); 3.75 (s, 3H, –O—$\underline{CH_3}$); 4.99 (d, 1H, J = 3.9 Hz); 7.24 (s, 1H, –CO–$\underline{NH}$–); 7.25 (s, 1H, –CO–$\underline{NH}$–).
^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 16.8/17.5 (–CO–O–CH–CH–$(\underline{CH_3})_2$); 18.8/17.5 (–NH–CH–CH–$(\underline{CH_3})_2$); 28.6/28.7 ($(\underline{CH_3})_3$C–); 30.4/31.5 (–$\underline{CH}$–$(CH_3)_2$); 35.9 (–$\underline{CH_2}$–); 50.9 (–O–$\underline{CH_3}$); 51.5/52.5 (–$\underline{C}(CH_3)_3$); 57.1 (–$\underline{CH}$–CH_2–); 66.9 (–CO–$\underline{CH}$–NH–); 78.8 (–O–$\underline{CH}$–); 168.3/170.2/173.1 (–$\underline{CO}$–).
GC-MS (EI, 70eV): m/z (%): 458 (0.5, M^+), 357 (100).
Microanalysis: calcd for $C_{23}H_{43}N_3O_6$ (457.61) C: 60.37; H: 9.47; N: 9.18; found C: 59.93; H: 9.50; N: 9.29.

General procedure for the synthesis of compounds (15) and (16):

5 mmol amino acid are suspended in 50 ml methanol. After addition of 5 ml chloroacetaldehyde as a 45 % aqueous solution. 5 mmol methylisocyanide are slowly added to the stirred solution.

N-(1-(N-Methylcarbamoyl)-2-chlorethyl)-L-alanine methyl ester (15)

Yield: 0.44 g = 40 %; yellow oil. Diastereomeric excess: 35 %.
^{1} H-NMR (360 MHz, $CDCl_3$): δ = 1.38 (d, 3H, $\underline{CH_3}$–CH–, J = 7.1 Hz); 2.82 (d, 3H, $\underline{CH}_3$–NH–CO–, J = 5.0 Hz); 3.44 (t, 1H, CH_2–$\underline{CH}$–, J = 4.0 Hz), 3.49 (q, 1H, CH_3–$\underline{CH}$–, J = 7.1 Hz); 3,73 (s, 3H, $\underline{CH_3}$-O–); 3.87 – 3.91 (m, 2H, –$\underline{CH_2}$–Cl); 7.7 (br., 1H, –CO-$\underline{NH}$–CH_3).
^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 18.3 ($\underline{CH_3}$–CH–); 25.9 ($\underline{CH_3}$–NH–CO–); 46.0 (–$\underline{CH_2}$–Cl); 52.0 (–$\underline{CH_3}$–O–); 55.3 (CH_3–$\underline{CH}$–); 61.2 (–CH_2–$\underline{CH}$–); 175/171 (–$\underline{CO}$–NH– / –$\underline{CO}$–O–)
GC-MS (CI): m/z (%): 223 (96, MH^+), 187 (100, M^+-Cl).
Microanalysis: calcd for $C_8H_{15}N_2O_3Cl$ (222.67) C: 43.15; H: 6.79; N: 12.58; found C: 42.89; H: 6.97; N: 12.05.

N-(1-(N-Methylcarbamoyl)-2-chlorethyl)-L-valine methyl ester (16)

Yield: 0.58 = 42 %; yellow oil. Diastereomeric excess: 54 %.
^{1}H-NMR (360 MHz, $CDCl_3$): δ = 1.00 (d, 3H, $(\underline{CH_3})_2$–CH–, J = 6.5 Hz); 0.98 (d, 3H, $(\underline{CH_3})_2$–CH–, J = 6.5 Hz); 2.10 (m, 1H, $(CH_3)_2$–$\underline{CH}$–, J = 6.5 Hz); 2.84 (d, 3H, $\underline{CH}_3$–NH–CO–, J = 5.2 Hz); 3.22 (d, 1H,

$(CH_3)_2$–CH–CH–, J = 5.2 Hz); 3.37 (t, 1H, $-CH_2-CH-$, J = 4.6 Hz), 3.72 (s, 3H, CH_3–O–), 3.80 (dd, 1H, $-CH_2$–Cl, J = 11.0 / 3.9 Hz); 3.96 (dd, 1H, $-CH_2$–Cl, J = 11.0 / 5.2 Hz); 7.6 (br.,1H, –CO–NH–CH_3).

^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 17.9 ($(CH_3)_2$–CH–); 19.2 ($(CH_3)_2$–CH–); 25.7 (CH_3–NH–CO–); 31.0 ($(CH_3)2$–CH–); 45.3 ($-CH_2$–Cl); 51.6 (CH_3–O–); 61.8 ($(CH_3)_2$–CH–CH–); 65.9 ($-CH_2-CH-$); 174/170 (–CO–NH– / –CO–O–)

GC-MS (CI): m/z (%): 251 (80, MH^+), 215 (100, M^+-Cl).

Microanalysis: calcd for $C_{10}H_{19}N_2O_3Cl$ (250.73) C: 47.91; H: 7.64; N: 11.17; found C: 47.56; H: 7.75; N: 11.13.

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