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A NEW CLASS OF CONVERTIBLE ISOCYANIDES IN THE UGI FOUR-COMPONENT REACTION

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Abstract: *The synthesis of a new class of isocyanides and its application in the Ugi reaction is described. Ugi products derived from (β-isocyano-ethyl)-alkyl-carbonates can be converted to N-acylated α-amino acids and esters under mild basic conditions.*

Keywords: Isocyanides; Ugi-Passerini Reactions; Cleavage reactions; Amino acids and derivatives

The Ugi four component reaction (U-4CR)[1] is a well known method to generate α-aminoacyl-amides from isocyanides, aldehydes, amines and a carboxylic acids in a one-pot synthesis. Due to the great diversity of products which can be obtained by this reaction, the U-4CR is an important tool in combinatorial chemistry[2]. Several researchers have focused on the U-4CR to prepare libraries of Ugi products[3].

At the moment, there is no practical way to prepare the important class of α-amino acids and esters[4] via Ugi reaction. The problem is the conversion of the secondary amide of the Ugi products into a carboxylic acid or ester under mild conditions.

Armstrong et al[5] synthesised certain α-aminoacyl-amides **1** (Scheme 1) using 1-cyclohexenyl isocyanide[6]. Subsequently, they were able to convert the thus created secondary amide moieties into carboxylic acids, esters or thioesters under weak acidic conditions. Protonation of the enamide yields a reactive intermediate **2** which cyclizes to a münchnone **3** by eliminating cyclohexene imine. **3** undergoes ring opening by nucleophilic attack of water, alcohols or thiols.

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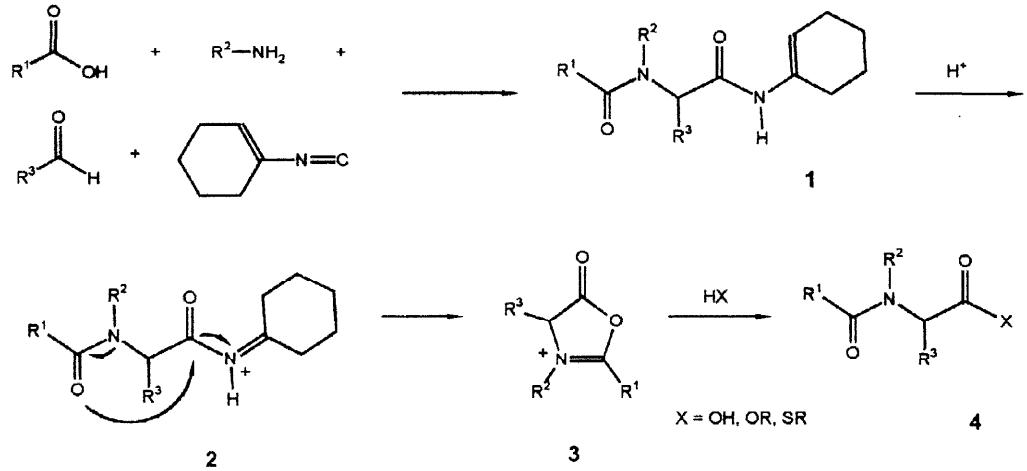
An electron rich N-acyl-moiety is essential for the formation of the münchnone. In case the Ugi product does not contain an N-acyl- or just an N-formyl-function no cyclization to **3** occurs. Cleavage exclusively leads to the primary amide.

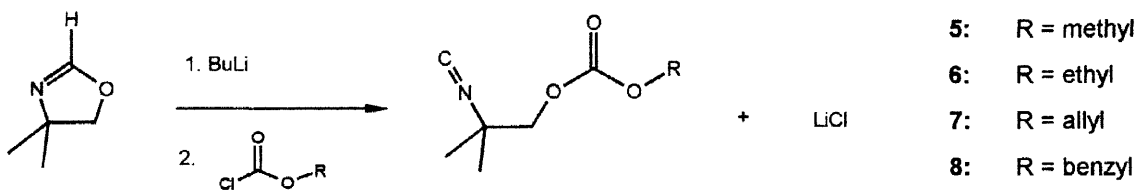
Scheme 1



The 1-cyclohexenyl isocyanide method to convert the secondary amide moiety is dependent on the structure of the Ugi product. Additionally, synthesis of 1-cyclohexenyl isocyanide is quite laborious and it is only stable for a few months if it is stored under argon at -30°C. As a consequence, the general applicability of 1-cyclohexenyl isocyanide is questionable.

We here report the development of (β-isocyano-ethyl)-alkyl-carbonates **5-8**[7,8] representing a new class of isocyanides (Scheme 2). Their application in the U-4CR and subsequent cleavage offers easy access to α-amino acids and α-amino acid esters.

Scheme 2

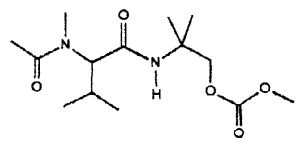
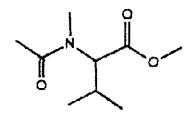
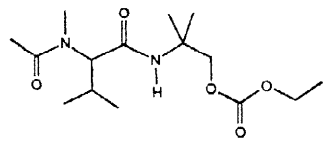
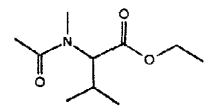
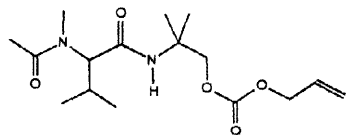
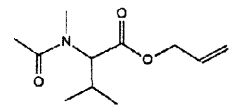
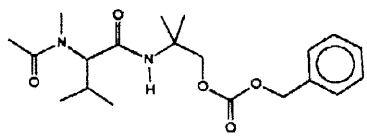
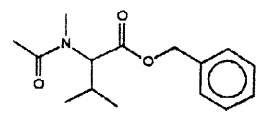
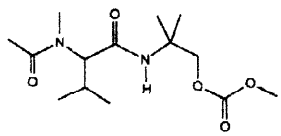
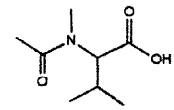
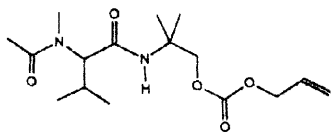
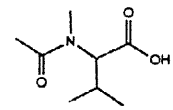
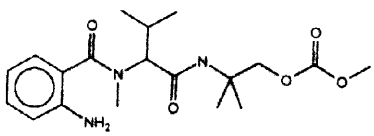
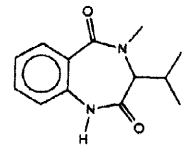


The synthesis of the (β-isocyano-ethyl)-alkyl-carbonates is very simple. 4,4-Dimethyl-2-oxazoline is deprotonated with BuLi in absolute THF at -78°C. The resulting lithium alcoholate is captured with an alkyl chloroformate to provide **5-8** in yields of up to 80%. **5**, **6** and **7** can be purified by vacuum distillation.

This new class of isocyanides offers several advantages. Their one-step synthesis from commercially available compounds facilitates large-scale production and does not involve the use of phosgene or its derivatives. Furthermore, (β-isocyano-ethyl)-alkyl-carbonates are stable and storable at room temperature.

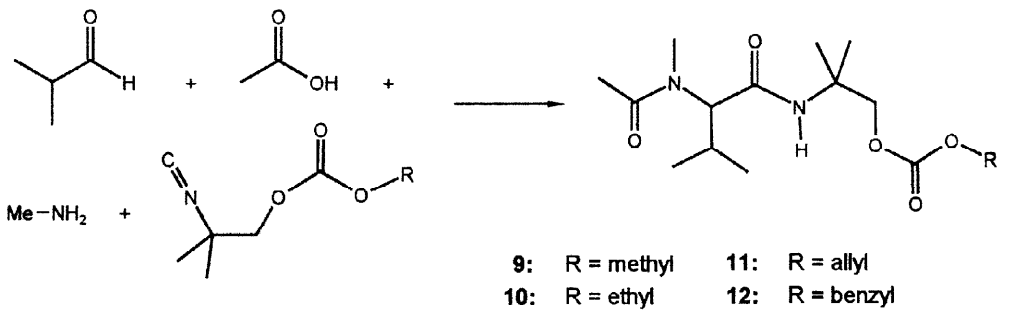
The results of several U-4CRs using isobutyraldehyde, methyl amine, acetic acid and **5-8**[7] are shown in Table 1. The Ugi products **9-12** can be converted to carboxylic esters **13-16** in good yields by treatment with potassium tert-butoxide.

Table 1:

Ugi Product		Yield	Base	Cleavage Product		Yield
	**9**	90%	K t-BuO		**13**	85%
	**10**	87%	K t-BuO		**14**	78%
	**11**	88%	K t-BuO		**15**	31%
	**12**	80%	K t-BuO		**16**	75%
	**9**	90%	K t-BuO / H_2O		**17**	70%
	**11**	88%	K t-BuO / H_2O		**17**	70%
	**18**	--	K t-BuO		**19**	61%

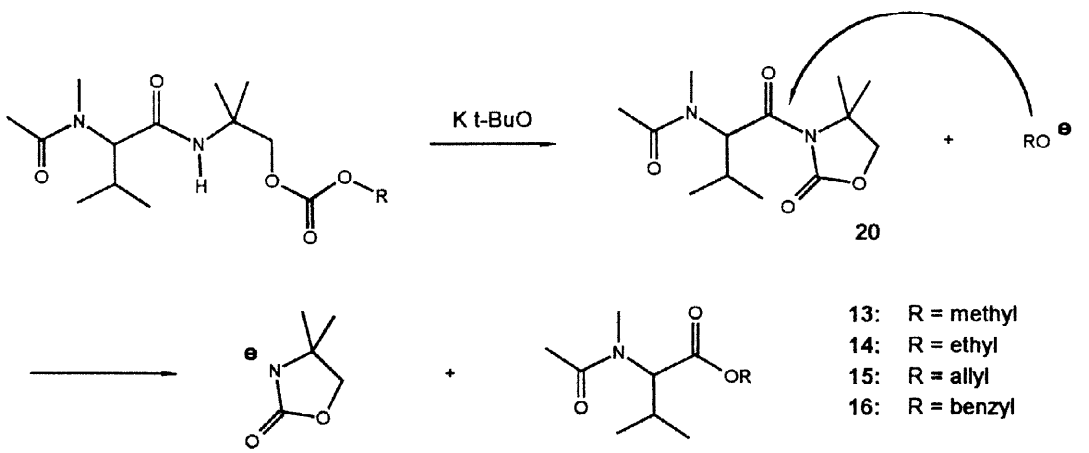
Reaction of methyl amine, isobutyraldehyde, acetic aid and the new isocyanides **5-8** provides the Ugi products **9-12** (Scheme 3).

Scheme 3



The cleavage reaction proceeds in absolute THF at room temperature. The postulated mechanism for the basic cleavage is shown in Scheme 4.

Scheme 4



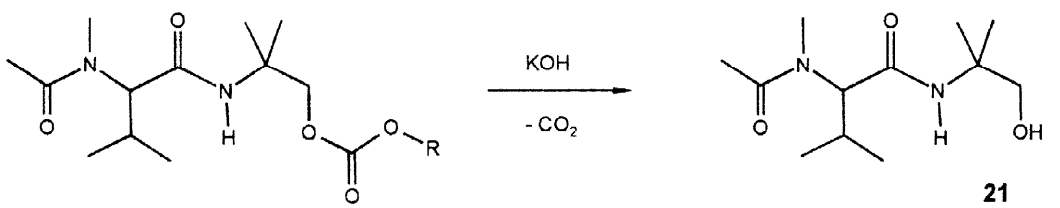
The first step is the abstraction of the secondary amide proton by potassium tert-butoxide followed by an intramolecular cyclization to provide a cyclic N-acyl urethane **20**. It is known that **20** can easily be cleaved[9]. The alcoholate that was liberated during the cyclization now converts **20** in situ in the 4,4-dimethyl-2-oxazoline-2-one anion and the corresponding α-amino acid esters **13-16**.

Ugi products **9** or **11** can each be converted to the carboxylic acid as well by synthesising the corresponding esters **13** or **15** with potassium tert-butoxide which then are saponified to **17** in situ by addition of water.

When converting **11** to **15**, the allylic ester **15** is only obtained with a yield of 31 %. Even under anhydrous conditions the potassium salt of **17** is isolated as a further product. This surprising formation of the potassium carboxylate is subject of further investigations.

We also examined the potential of our new method in the synthesis of 1,4-benzodiazepine-2,5-diones. Reaction of anthranilic acid, isobutyraldehyde methyl amine and **5** provides Ugi product **18** which is very sensitive to polymerisation. Therefore, it is advantageous to convert **18** into **19** immediately after work up by treatment with potassium tert-butoxide in absolute THF. The intermediate methyl ester was not detected during the reaction due to rapid cyclization of this compound to **19** in an overall yield of 61%. During the Preparation of the cyclic N-acyl urethane anhydrous conditions are essential. Presence of KOH leads to partial saponification of the carbonate moiety and liberation of carbon dioxide prior to the intramolecular cyclization resulting in the formation of **21** (Scheme 5).

Scheme 5



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In summary, a new and practical method for the synthesis of α-acylamino-acids and esters via Ugi reaction with a new class of easily accessible isocyanides is described. Basic conversion of the Ugi products, derived from (β-isocyano-ethyl)-alkyl-carbonates, to α-amino acids or esters is not limited by the structure of the residual molecule. The scope of this class of isocyanides in the Passerini reaction (generating α-acyloxy acids and esters) and in the Ugi five-center-four-component reaction (U-5C-4CR)[10] which yields 1,1'-Iminodicarboxylic acids and esters is being investigated and the results will be reported soon. We believe that these new functionalities in combination with all kinds of isocyanide based multi component reactions have a huge potential in creating new molecules or simplifying the synthesis of existing compounds.

Experimental

Reagents were obtained from commercial sources and used as received. THF was dried and distilled from sodium/benzophenone.

NMR spectra were recorded in $CDCl_3$ on Bruker spectrometers AM 250 with TMS as internal standard. The chemical shifts are reported in ppm downfield from TMS. Coupling constants are listed in hertz. GC-MS were performed on a varian MAT CH-5 apparatus coupled to a GC Carlo Erba 4160 column.

General procedure for the synthesis of [(2-isocyano–2-methyl)-propyl-1-]-alkyl-carbonates 5-8

BuLi (200 mmol) is added slowly to 4,4-dimetyl-2-oxazoline (200 mmol) in 200 ml dry THF at -78°C. The solution is stirred for 1 h at -78°C and chloroformate (200 mmol) is added dropwise. After 30 minutes the solution is allowed to reach 25°C. The solution is washed with water and saturated aqueous NaCl and dried over anhydrous Na_2SO_4. Removal of the solvent yields colourless oils (yield: 80%), which were used in the U-4CR without further purification.

The methyl-, ethyl- and allyl-derivatives of [(2-isocyano–2-methyl)-propyl-1-]-alkyl-carbonates can be purified by distillation.

[(2-Isocyano–2-methyl)-propyl-1-]-methyl-carbonate 5

colourless crystals, $bp_{0.1torr}$52-53°C, mp: 31°C. **IR** (neat): 2959, 2137, 1755, 1270 cm^{-1}; **^{1}H-NMR:** δ = 4.10 (m, 2H); 3.83 (s, 3H); 1.47 (m, 6H); **^{13}C-NMR:** δ = 156.1; 155.2; 72.6; 56.2; 55.1; 25.7;

[(2-Isocyano–2-methyl)-propyl-1-]-ethyl-carbonate 6

colourless liquid, $bp_{0.03torr}$46-47°C. **IR** (neat): 2983, 2135, 1751, 1263 cm^{-1}; **^{1}H-NMR:** δ = 4.24 (q, 2H, J= 7.1); 4.09 (m, 2H); 1.48 (m, 6H); 1.34 (tr, 3H, J= 7.1); **^{13}C-NMR:** δ = 155.9; 154.6; 72.3; 64.5; 56.1; 25.7; 14.1;

[(2-Isocyano–2-methyl)-propyl-1-]-allyl-carbonate 7

colourless liquid, $bp_{0.1torr}$75-76°C. **IR** (neat): 2958, 2136, 1753, 1261 cm^{-1}; **^{1}H-NMR:** δ = 5.93 (m, 1H); 5.35 (m, 2H); 4.66 (m, 2H); 4.11 (m, 2H); 1.47 (m, 6H); **^{13}C-NMR:** δ = 156.1; 154.5; 131.1; 119.3; 72.6; 68.9; 56.2; 25.8;

[(2-Isocyano–2-methyl)-propyl-1-]-benzyl-carbonate 8

colourless oil. **IR (neat)**: 3034, 2958, 2135, 1748, 1267 cm^{-1}; **^{1}H-NMR:** δ = 7.34 (m, 5H); 5.18 (m, 2H); 4.09 (m, 2H); 1.43 (m, 6H); **^{13}C-NMR:** δ = 156.2; 154.6; 134.8; 128.6; 128.5; 128.3; 72.6; 70.1; 56.1; 25.7;

General Procedure for the Ugi Reaction

Isobutyraldehyde (8 mmol), and methyl amine (8 mmol) are stirred in 16 ml of methanol at 25 °C for 2 h. (β-Isocyano–ethyl)-alkyl-carbonate (8 mmol) and acetic acid (8 mmol) are added and the mixture is stirred for 24 h at the same temperature. After removal of the solvent in vacuum, the product is isolated via flash column chromatography as a mixture of rotamers (silica, hexane/ethyl acetate 3:1). The data are given for the major rotamer.

(R,S)-N-[2-(2-methyl-propyl-1)]-methyl-carbonate-2-(N′-methylacetamido)-3-methylbutanamide 9

Yield: 90% (rotamers 9.2:1); **IR** (KBr): 3283, 2965, 1745, 1678, 1627 cm^{-1}; **^{1}H-NMR:** δ = 6.22 (s_{br}, 1H); 4.45 (d, 1H); 4.36 (d, 1H, J= 10.4); 4.20 (d, 1H, J= 10.4); 2.94 (s, 3H); 2.22 (m, 1H); 2.14 (s, 3H); 1.35 (s, 3H); 1.28 (s, 3H); 0.95 (d, 3H, J= 6.7); 0.81 (d, 3H, J= 6.7); **^{13}C-NMR:** δ = 172.2; 169.8; 155.6; 71.2; 62.8; 54.8; 53.0; 31.3; 25.0; 24.3; 23.8; 22.0; 19.5; 18.5; **GC-MS** (EI), m/z (%): 302 (17, M^+); 156 (26); 128 (95); 86 (100); $C_{14}H_{26}N_2O_5$;

(R,S)-N-[2-(2-methyl-propyl-1)]-ethyl-carbonate-2-(N′-methylacetamido)-3-methylbutanamide 10

Yield: 87% (rotamers 9.0:1); **IR** (neat): 3320, 2972, 1748, 1681, 1631 cm^{-1}; **^{1}H-NMR:** δ = 6.14 (s_{br}, 1H); 4.45 (d, 1H, J= 11.0); 4.34 (d, 1H, J= 10.4); 4.17 (m, 4H); 2.93 (s, 3H); 2.23 (m, 1H); 2.14 (s, 3H); 1.35 (s, 3H); 1.32 (tr, 3H); 1.28 (s, 3H); 0.95 (d,
3H, J= 6.5); 0.81 (d, 3H, J= 6.5); **^{13}C-NMR:** δ = 172.3; 169.7; 155.0; 70.8; 64.0; 62.7; 53.0; 31.2; 25.4; 24.5; 23.8; 21.9; 19.5; 18.5; 14.2; **GC-MS** (EI), m/z (%): 316 (20, M^+); 156 (35); 128 (96); 86 (100); $C_{15}H_{28}N_2O_5$;

(R,S)-N-[2-(2-methyl-propyl-1)]-allyl-carbonate-2-(N′-methylacetamido)-3-methylbutanamide 11

Yield: 88% (rotamers 3.2:1); **IR** (KBr): 3312, 3065, 2967, 1743, 1680, 1629 cm^{-1}; **^{1}H-NMR:** δ = 6.22 (s_{br}, 1H); 5.91 (m, 1H); 5.32 (m, 2H); 4.62 (m, 2H); 4.46 (d, 1H,); 4.37 (d, 1H, J= 10.5); 4.21 (d, 1H, J= 10.5); 2.93 (s, 3H); 2.22 (m, 1H); 2.13 (s, 3H); 1.35 (s, 3H); 1.28 (s, 3H); 0.95 (d, 3H, J= 6.4); 0.81 (d,

3H, J= 6.4); **^{13}C-NMR:** δ = 172.4; 169.9; 155.6; 131.6; 119.1; 71.1; 68.5; 62.9; 53.0; 31.6; 25.6; 24.7; 23.9; 22.0; 19.6; 18.6; **GC-MS** (EI), m/z (%): 328 (3, M^+); 156 (18); 128 (97); 86 (100); $C_{16}H_{28}N_2O_5$;

(R,S)-N-[2-(2-methyl-propyl-1)]-benzyl-carbonate-2-(N′-methylacetamido)-3-methylbutanamide 12

Yield: 80% (no rotamers); **IR** (neat): 3309, 3034, 2964, 1749, 1679, 1631 cm^{-1}; **^{1}H-NMR:** δ = 7.36 (m, 5H); 6.16 (s_{br}, 1H); 5.15 (m, 2H); 4.30 (m, 3H); 2.89 (s, 3H); 2.21 (m, 1H); 2.03 (s, 3H); 1.36 (s, 3H); 1.27 (s, 3H); 0.96 (d, 3H, J= 6.7); 0.79 (d, 3H, J= 6.7);

^{13}C-NMR: δ = 172.3; 169.8; 155.0; 135.2; 128.6; 128.5; 128.4; 71.1; 69.7; 62.7; 53.0; 31.2; 25.5; 24.7; 23.8; 21.9; 19.5; 18.5; **GC-MS** (EI), m/z (%): 378 (7, M^+); 153 (9); 141 (12); 128 (100); 86 (64); $C_{20}H_{30}N_2O_5$;

General Procedure for the synthesis of (R,S)-2-(N-(methyl)acetamido)-3-methylbutanoic acid esters 13-16

The Ugi-product (5 mmole) and potassium tert-butoxide (6 mmole) are stirred in 15 ml of anhydrous THF at 25 °C. When the reaction is complete as indicated by TLC (hexane/ethyl acetate 3:1) conc. HCl (6 mmole) is added. After removal of the solvent in vacuum, the product is isolated via flash column chromatography as a mixture of rotamers (silica, hexanes/ethyl acetate 3:1).

(R,S)-2-(N-(methyl)acetamido)-3-methylbutanoic acid methyl ester 13

Yield: 80% (rotamers 2.2:1); **IR** (neat): 2966, 1738, 1651 cm^{-1}; **^{1}H-NMR:** δ = 4.96 (d, 1H,); 3.70 (s, 3H); 2.99 (s, 3H); 2.22 (m, 1H); 2.14 (s, 3H); 0.99 (d, 3H, J= 6.5); 0.87 (d, 3H, J= 6.5); **^{13}C-NMR:** δ = 171.6; 171.4; 60.9; 51.6; 31.9; 27.4; 21.8; 19.5; 18.8; **GC-MS** (EI), m/z (%): 187 (20, M^+); 128 (90); 102 (86); 86 (100); 74 (34); $C_9H_{17}NO_3$;

(R,S)-2-(N-(methyl)acetamido)-3-methylbutanoic acid ethyl ester 14

Yield: 78% (rotamers 1.9:1); **IR** (neat): 2967, 1736, 1654 cm^{-1}; **^{1}H-NMR:** δ = 4.92 (d, 1H,); 4.18 (m, 2H); 3.00 (s, 3H); 2.24 (m, 1H); 2.14 (s, 3H); 1.26 (m, 3H); 1.01 (d, 3H, J= 6.7); 0.87 (d, 3H, J= 6.7); **^{13}C-NMR:** δ = 171.4; 171.1; 60.; 60.4; 31.8; 27.2; 21.6; 19.3; 18.7; 13.9; **GC-MS** (EI), m/z (%): 201 (36, M^+); 128 (96); 116 (82); 86 (100); 74 (36); $C_{10}H_{19}NO_3$;

(R,S)-2-(N-(methyl)acetamido)-3-methylbutanoic acid allyl ester 15

Yield: 31% (rotamers 2.0:1); **IR** (neat): 3086, 2965, 1736, 1658 cm^{-1}; **^{1}H-NMR:** δ = 5.75 (m, 1H); 5.10 (m, 2H); 4.81 (d, 1H,); 4.47 (m, 2H); 2.85 (s, 3H); 2.08 (m, 1H); 1.98 (s, 3H); 0.87 (d, 3H, J= 6.5); 0.73 (d, 3H, J= 6.5); **^{13}C-NMR:** δ = 170.8; 170.3; 131.4; 117.9; 64.7; 60.7; 31.7; 27.1; 21.4; 19.1; 18.5; **GC-MS** (EI), m/z (%): 263 (1, M^+); 178 (6); 128 (58); 86 (100); $C_{15}H_{21}NO_3$;

(R,S)-2-(N-(methyl)acetamido)-3-methylbutanoic acid benzyl ester 16

Yield: 75% (rotamers 2.0:1); **IR** (neat): 3033, 2965, 1737, 1656 cm^{-1}; **^{1}H-NMR:** δ = 7.35 (m, 5H); 5.15 (m, 2H); 4.89 (d, 1H,); 2.90 (s, 3H); 2.21 (m, 1H); 2.09 (s, 3H); 0.97 (d, 3H, J= 6.7); 0.85 (d, 3H, J= 6.7); **^{13}C-NMR:** δ = 171.4; 170.9; 135.6;

128.4; 128.1; 128,0; 66.3; 61.0; 32.0; 27.4; 21.8; 19.5; 18.8; **GC-MS** (EI), m/z (%): 213 (2, M^+); 128 (66); 86 (100); $C_{11}H_{19}NO_3$;

(R,S)-3-Isopropyl-4-methyl-1,4-benzodiazepine-2,5-dione 19

Isobutyraldehyde (4 mmol) and methyl amine (4 mmol) are stirred in 8 ml of methanol for 2 h at 25 °C. **5** (4 mmol) and anthranilic acid (4 mmol) are added and the mixture is stirred for 24 h at the same temperature. After removal of the solvent in vacuum at 45°C, the products are stirred in 15 ml of anhydrous THF with potassium tert-butoxide (5 mmol) at 25 °C. When the reaction is complete as indicated by TLC (hexanes/ethyl acetate 3:1) conc. HCl (5 mmol) is added. After removal of the solvent in vacuum, the product is isolated via flash column chromatography as a mixture of tautomers (silica, hexane/ethyl acetate 3:1).

Yield: 61% (tautomers, 4.2:1); **IR** (KBr): 3432, 2961, 1685, 1610 cm^{-1}; **^{1}H-NMR:** δ = 9.88 (s_{br}, 1H); 7.96 (m, 1H); 7.38 (m, 1H); 7.20 (m, 1H); 7.02 (m, 1H); 3.57 (m, 1H); 3.31 (s, 3H); 1.72 (m, 1H); 0.88 (m, 6H); **^{13}C-NMR:** δ = 171.8; 165.9; 134.6; 132.3; 131.2; 126.4; 124.6; 120.0; 73.8; 40.2; 27.7; 19.5; 19.2; **GC-MS** (EI), m/z (%): 232 (82, M^+); 189 (100); 161 (68); 148 (88); 86 (38); 42 (54); $C_{13}H_{16}N_2O_2$;

General Procedure for the synthesis of (R,S)-2-(N-(methyl)acetamido)-3-methylbutanoic acid 17

9 respectively **11** (5 mmol) and potassium tert-butoxide (6 mmol) are stirred in 15 ml of anhydrous THF at 25 °C. When the reaction is complete as indicated by TLC (hexanes/ethyl acetate 3:1) 0.9 ml of water is added. After saponification is finished as indicated by TLC, the solution is neutralised by adding conc. HCl (6 mmol). After removal of the solvent in vacuum, the product is isolated via flash column

chromatography as a mixture of rotamers (silica, first hexane/ethyl acetate 3:1, then $CHCl_3$, MeOH, AcOH 100:10:1).

Yield: 70% (rotamers 1.6:1); **IR (KBr)**: 2967, 2586, 1731, 1606 cm^{-1}; **^{1}H-NMR:** δ = 10.75 (s_{br}, 1H); 4.93 (d, 1H,); 3.02 (s, 3H); 2.22 (m, 1H); 2.17 (s, 3H); 1.05 (d, 3H, J= 6.5); 0.88 (d, 3H, J= 6.5); **^{13}C-NMR:** δ = 173.1; 172.7; 62.2; 32.8; 27.2; 21.5; 19.6; 18.9;

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