Scientific paper

Synthesis of Novel 3D-Rich α-Amino Acid-Derived 3-Pyrazolidinones

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Dedicated to Professor Emeritus Miha Tišler, University of Ljubljana, on the occasion of his 90th birthday.

Abstract

Synthetic approaches towards novel 3-pyrazolidinone derivatives functionalized at positions N(1) and/or C(5) were studied. 5-Aminoalkyl-3-pyrazolidinones were prepared in four steps from *N*-protected glycines via *Masamune-Claisen* homologation, reduction, O-mesylation, and cyclisation with a hydrazine derivative. The free amines were prepared by acidolytic deprotection. Title compound was also prepared by 'ring switching' transformation of *N*-Boc-pyrrolin-2(5*H*)-one with hydrazine hydrate. Hydrogenolytic deprotection of 5-(*N*-alkyl-*N*-Cbz-aminomethyl)pyrazolidine-3-ones followed by cyclisation with 1,1'-carbonyldiimidazole (CDI) gave two novel representatives of perhydroimidazo[1,5-*b*]pyrazole, which is an almost unexplored heterocyclic system. Amidation of 3-oxopyrazolidine-5-carboxylic acid gave the corresponding carboxamides in moderate yields. Diastereomeric non-racemic carboxamides obtained from (*S*)-AlaOMe and (*S*)-ProOMe were separated by MPLC.

Keywords: 3-Pyrazolidinones, amino acids, cyclization, heterocycles, synthesis

1. Introduction

Hetero(bi)cycles are commonly used building blocks for applications in medicinal chemistry, catalysis, and materials science.[1,2] In this context, 3-pyrazolidinones and their bicyclic analogues are attractive targets due to their easy availability from α,β-unsaturated esters and because of their applicability and biological activity.[3–6] Pyrazolidinone derivatives have been employed as dyes and photographic developers[3,5] and as inhibitors of cyclooxygenase, lipoxygenase,[7] and γ-aminobutyrate aminotransferase[8] exhibiting analgesic, antipyretic, anti-inflammatory, and anorectic activity. Among bicyclic analogues, perhydropyrazolo[1,2–*a*]pyrazolones belong to azabicycloalkane amino acids, which are U-shaped conformationally constrained heterocyclic analogues of peptides that simulate β-turn structures.[9,10] Consequently, bicyclic pyrazolidinones are used as drugs to relieve Alzheimer's disease[11] and as antibacterial (Eli-Lilly's γ-lactam antibiotics),[12] and antitrypanosomal agents.[13] Synthetic applications of 3-pyrazolidinones comprise their use as chiral auxiliaries,[14–19] as templates in asymmetric Diels-Alder cycloadditions,[20–22] and as a new scaffold in organocatalysis.[23–30] Typical examples of important 3-pyrazolidinone derivatives are depicted in Figure 1.

However, in spite of easy availability of simple pyrazolidinones from α,β-unsaturated esters and hydrazine derivatives,[3–6,31,32] the synthesis of functionalized polysubstituted pyrazolidinones remains challenging. Consequently, a majority of saturated bi- and tricyclic 3-pyrazolidinones are either unknown or unexplored heterocyclic systems.

In the context of our ongoing work on the synthesis of chiral heterocycles with emphasis on pyrazole[33,34] and pyrazolidinone derivatives,[31,32] we reported the synthesis of tetrahydropyrazolo[1,5–*c*]pyrimidine-2,7-diones as the first representatives of a novel saturated heterocyclic system,[35,36] followed by preparation of closely related tetrahydropyrazolo[1,5–*c*]pyrimidine-3-carboxamides[37] and tetrahydro-1*H*-imidazo[1,5–*b*]pyrazole-2,6-diones.[38] In ex-

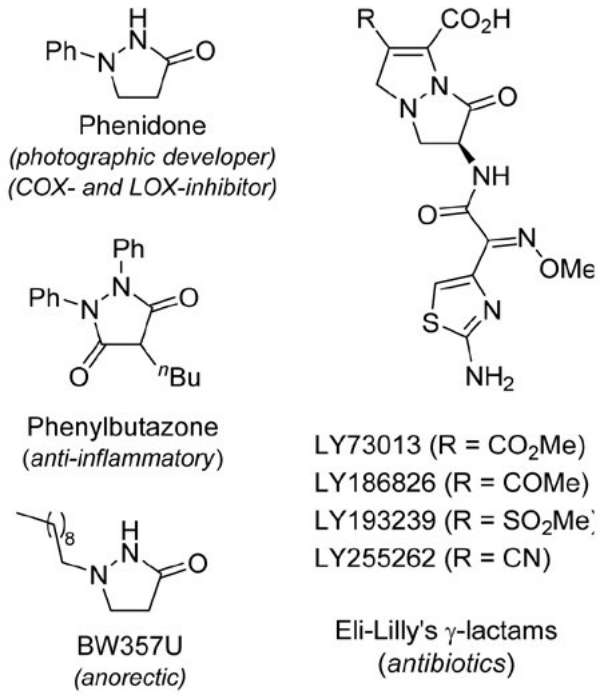
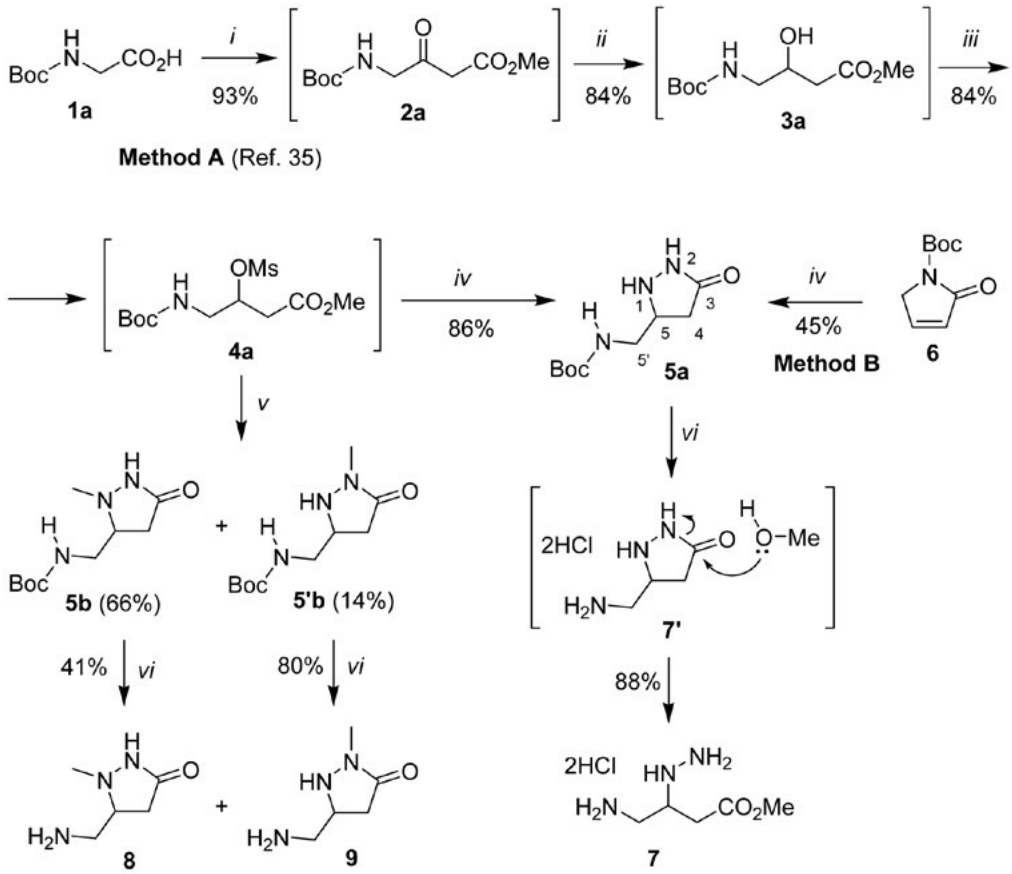


Figure 1. Examples of important 3-pyrazolidinone derivatives.

tension, the first representatives of octahydro-2*H*-2a,2a[1]-diazacyclopenta[*cd*]inden-2-one as a novel tricyclic pyrazolidinone-based system were also prepared.[39] Crucial for all of the above syntheses was the preparation of a pyrazolidinone key-intermediate with suitably functionalized substituent at position 5 allowing for cyclization to position 1. The 5-substituted pyrazolidinone was obtained by cyclization of the corresponding *β*-mesyloxy ester, which in turn was obtained in three steps from a suitably functionalized carboxylic acid.[31] Pyrazolidinones with 2-hydroxyethyl[36] and 2-aminoethyl[35,37] functional groups at position 5 were used as key intermediates in the synthesis of novel saturated heterocyclic systems, while 5-[(*S*)-1-aminoalkyl] derivatives prepared from *N*-protected α-amino acids were used as scaffolds for potential organocatalysts[38] and as key-intermediates in the synthesis of 3-pyrrolinones.[40]

In addition to previously published 5-aminoethyl and 5-hydroxymethyl-3-pyrazolidinones, we also tried to prepare the 5-aminomethyl analogues, because they could be useful intermediates in the synthesis of novel saturated heterocycles in the imidazo[1,5–*b*]pyrazole and pyrazolo[1,5–*a*]pyrazine series. In this paper, we report the preparation and some follow-up transformations of 5-ami-

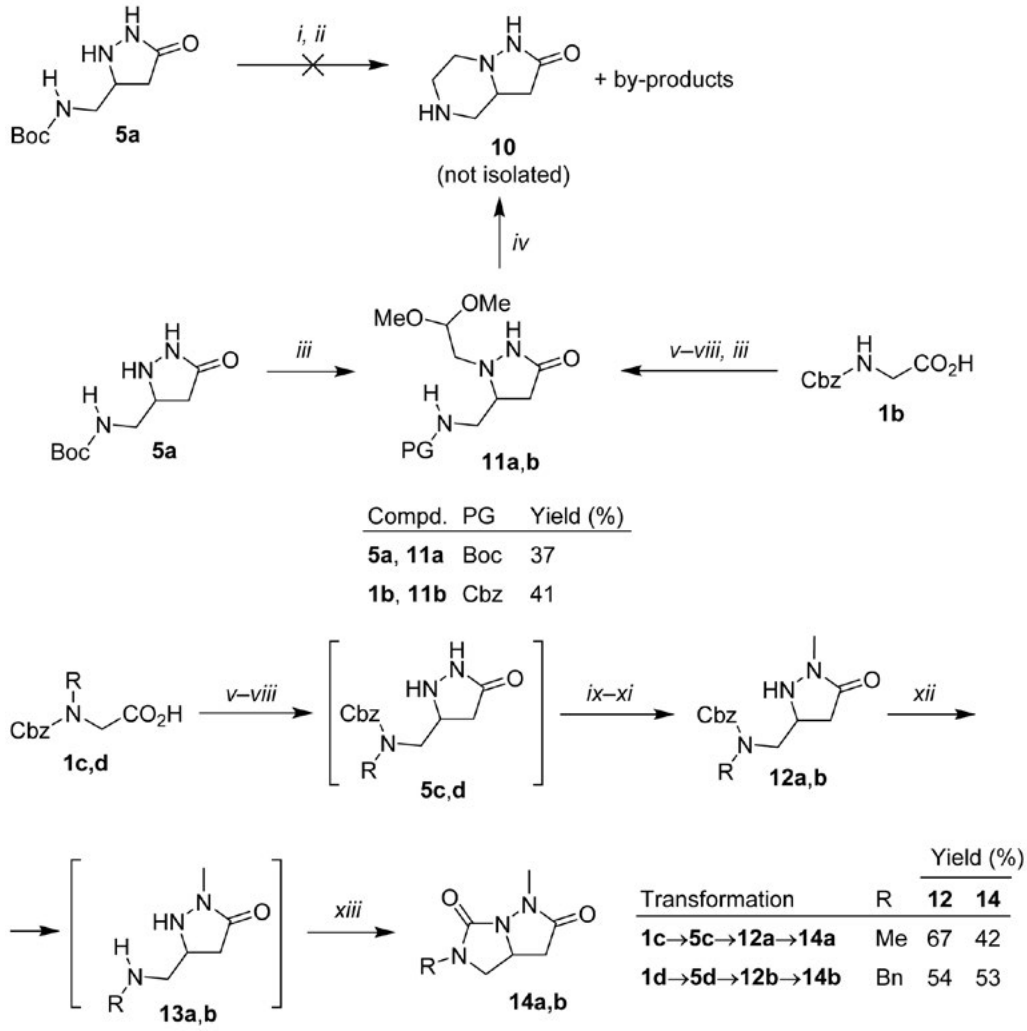


Scheme 1. Synthesis of the 5-aminomethyl-3-pyrazolidinones **5a**, **5b**, **5'b**, and **7–9**. Reaction conditions: *i*) CDI, THF, r.t. 2 h, then $MeO_2CCH_2CO_2K$, $MgCl_2$, r.t.; *ii*) $NaBH_4$, MeOH, 0–20 °C; *iii*) MsCl, pyridine, CH_2Cl_2, 0 °C; *iv*) $N_2H_4{\cdot}H_2O$, MeOH, r.t.; *v*) $MeNHNH_2$, MeOH, r.t., then chromatographic separation (MPLC); *vi*) HCl-EtOAc, MeOH, r.t.

nomethyl and 5-carboxy substituted 3-pyrazolidinones available from glycine derivatives and from dimethyl maleate, respectively. These novel pyrazolidinone derivatives are interesting intermediates in the synthesis of chiral saturated pyrazolidine-based heterocyclic systems.

2. Results and Discussion

First, 5-*tert*-butoxycarbonylaminomethyl-3-pyrazolidinones **5a**, **5b**, and **5'b** were prepared in four steps from commercially available *N*-Boc-glycine (**1a**) following a well-established literature protocol.[35–39] Masamune-Claisen condensation of amino acid **1a**, *i.e.* activation of **1a** with 1,1'-carbonyldiimidazole (CDI) followed by treatment of the intermediate imidazolide with a mixture of potassium monomethyl malonate and magnesium chloride gave the corresponding *β*-keto ester **2a** in 93% yield. Reduction of **2a** with $NaBH_4$ in methanol followed by *O*-mesylation of the so formed alcohol **3a** afforded the *β*-mesyloxy ester **4a** in 71% yield over two steps. The mesylate **4a** was then cyclized with hydrazine hydrate or methylhydrazine to furnish the N(5')-protected 5-aminomethyl-3-pyrazolidinones **5a**, **5b**, and **5'b**. Cyclisation of the mesylate **4a** with methylhydrazine was regioselective to give a ~5:1 mixture of the major 1-methyl regioisomer **5b** and the minor 2-methyl isomer **5'b**. Upon chromatographic separation (MPLC), the pure regioisomers **5b** and **5'b** were obtained in 66% and 14% yields, respectively. To shorten the synthetic procedure for the preparation of **5a**, commercially available *tert*-butyl 2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**6**) was treated with hydrazine hydrate in methanol at room temperature to afford the pyrazolidinone **5a** in 45% yield. However, in spite of its greater simplicity, the latter procedure was less effective in terms of product yield. Finally, the respective free amines **7**–**9** were prepared



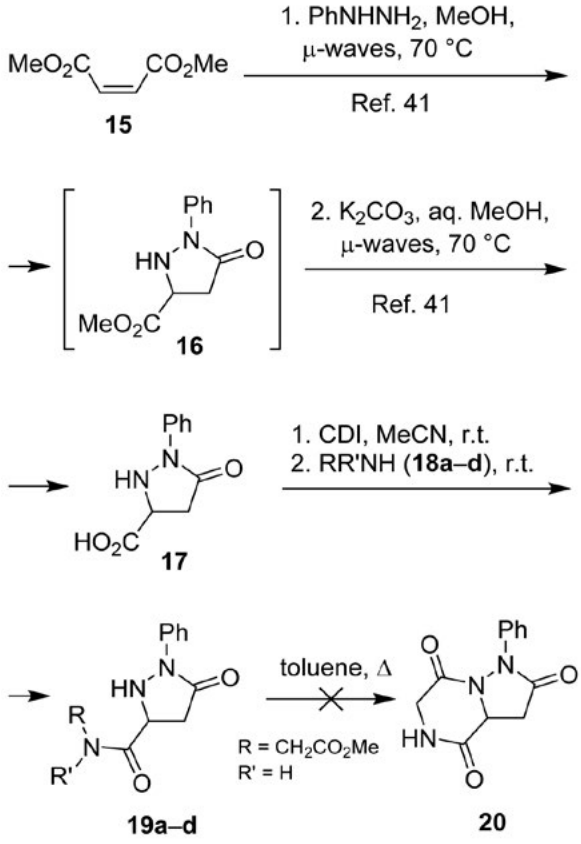
Scheme 2. Reaction conditions: *i*) TFA, CH_2Cl_2, r.t.; *ii*) 50% aq. glyoxal or $(MeO)_2CH_2CHO$, H_2, Pd-C, MeOH, r.t.; *iii*) 50% aq. $(MeO)_2CH_2CHO$, $NaBH_3CN$, MeOH, r.t.; *iv*) aq. HCl, MeOH, H_2, Pd-C, r.t.; *v*) CDI, THF, r.t. 2 h, then $MeO_2CCH_2CO_2K$, $MgCl_2$, r.t.; *vi*) $NaBH_4$, MeOH, 0–20 °C; *vii*) MsCl, pyridine, CH_2Cl_2, 0 °C; *viii*) $N_2H_4{\cdot}H_2O$, MeOH, r.t.; *ix*) Boc_2O, r.t.; *x*) MeI, DMF, K_2CO_3, r.t.; *xi*) TFA-CH_2Cl_2, r.t.; *xii*) H_2, Pd-C, MeOH, r.t.; *xiii*) CDI, DMF, r.t..

by acidolytic *N*-deprotection of **5a**, **5b**, and **5'b**. Quite unexpectedly, treatment of **5a** with HCl–MeOH gave the open-chain diamine **7**, which is explainable by acid-catalyzed ring-opening of the initially formed intermediate **7'** with methanol (Scheme 1).

Next, cyclisation of the pyrazolidinone **5a** was studied. Our initial goal was to prepare hexahydropyrazolo[1,5–*a*]pyrazin-2(1*H*)-one (**10**) by concomitant *N*-deprotection and reductive alkylation of **5a** with glyoxal or with dimethoxyacetaldehyde. Unfortunately, this approach did not work and furnished mixtures of products regardless of the variation of the reaction conditions. Nevertheless, we were able to detect the presence of the desired compound **10** in the crude reaction mixture by HRMS (m/z = 142.0974, MH^+). Attempted isolation and purification of this highly polar compound **10** failed. On the other hand, reductive alkylation of **5a** with dimethoxyacetaldehyde and $NaBH_3CN$ in methanol at room temperature gave the corresponding 1-(2,2-dimethoxyethyl) derivative **11a** in 37% yield. In the same way, the Cbz-analogue **11b** was prepared in five steps from *N*-Cbz-glycine (**1b**). Finally, two novel 1,5-dialkyltetrahydro-1*H*-imidazo[1,5–*b*]pyrazole-2,6-diones **14a** and **14b** were synthesized. Following the established one-pot protocol (*cf.* Scheme 1), *N*-Cbz-sarcosine (**1c**) and *N*-benzyl-*N*-Cbz-glycine (**1d**) were transformed in four steps into the corresponding pyrazolidinones **5c** and **5d**. In a subsequent one-pot procedure,[35] compounds **5c** and **5d** were Boc-protected at N(1), methylated at N(2), and Boc-deprotected to give the N(1)-unsubstituted intermediates **12a** and **12b** in good yields over seven steps. Somewhat expectedly,[38] cyclizations of **12a**,**b** into imidazo[1,5–*b*]pyrazole derivatives **14a**,**b** proceeded well. Hydrogenolytic deprotection of the pyrazolidinones **12a** and **12b** followed by cyclisation of the intermediate free amines **13** with CDI furnished the expected 1,5-dimethyltetrahydro-1*H*-imidazo[1,5–*b*]pyrazole-2,6-diones **14a** and **14b** in 42% and 53% yield, respectively (Scheme 2).

In continuation, the amidation of 5-oxo-1-phenylpyrazolidine-3-carboxylic acid (**17**) was studied. Compound **17** was obtained in three steps from dimethyl maleate (**15**) following the literature procedure.[41] Activation of the carboxylic acid **17** with CDI followed by treatment with primary amines **18a–c** gave the corresponding carboxamides **19a–c** in moderate yields. Somewhat surprisingly, amidation proceeded equally well with secondary diethylamine (**18d**) to afford the tertiary carboxamide **19d** in 49% yield. Attempted cyclisation of the glycine derivative **19a** into 1-phenyltetrahydropyrazolo[1,5–*a*]pyrazine-2,4,7(1*H*)-trione (**20**) in refluxing toluene failed (Scheme 3).

Finally, amidation of racemic carboxylic acid was also performed with the non-racemic α-amino esters, (*S*)-AlaOMe (**18e**) and (*S*)-ProOMe (**18f**). These amidations afforded mixtures of non-racemic diastereomers **19e/19'e** and **19f/19'f**. Subsequent separation of diastereomeric mixtures by medium pressure liquid chromatography furnished the non-racemic diastereomerically pure carboxamides



Compd.	R	R'	Yield (%)
18a, **19a**	CH_2CO_2Me	H	45
18b, **19b**	$CH_2CH_2CO_2Me$	H	45
18c, **19c**	CH_2CH_2Ph	H	50
18d, **19d**	Et	Et	49

Scheme 3. Synthesis of 3-pyrazolidinone-5-carboxamides **19a–d**.

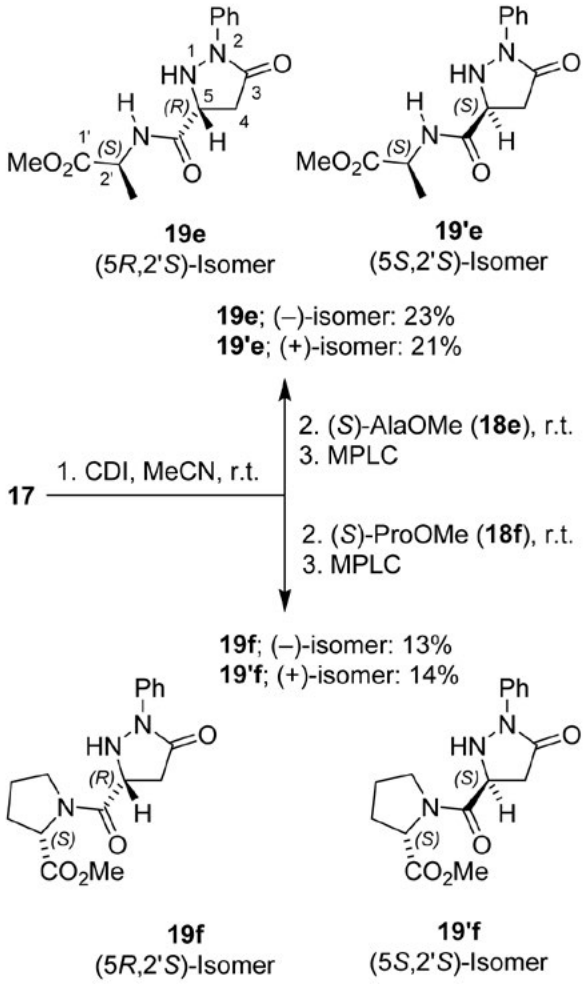
19e, **19'e**, **19f**, and **19'f** in 13–23% yields. Unfortunately, all products **19e**, **19'e**, **19f**, and **19'f** were obtained as oils and their absolute configuration could not be determined by X-ray diffraction. Therefore, the configurations of the products **19e**, **19'e**, **19f**, and **19'f** are arbitrary (Scheme 4).

The structures of novel compounds **5a**,**b**, **5'b**, **7–9**, **11a**,**b**, **14a**,**b**, **19a–f**, and **19'e**,**f** were determined by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR, MS, HRMS) and by elemental analyses for C, H, and N. Compounds **5b**, **5'b**, **8**, **9**, **11a**,**b**, **14a**,**b**, **19e**,**f**, and **19'e**,**f** were not obtained in analytically pure form. Their identities were confirmed by ^{13}C NMR and HRMS.

3. Experimental

3. 1. General Methods

Melting points were determined on a Stanford Research Systems MPA100 OptiMelt automated melting



Scheme 4. Synthesis of non-racemic 3-pyrazolidinones **19e**,**f** and **19'e**,**f**.

point system. The NMR spectra were obtained on a Bruker Avance III UltraShield 500 plus at 500 MHz for ^{1}H and 126 MHz for ^{13}C, using $CDCl_3$ and DMSO-d_6 (with TMS as the internal standard) as solvents. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS spectrometer, IR spectra on a Bruker FTIR Alpha Platinum ATR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN analyser 2400 II. Column chromatography (CC) was performed on silica gel (Fluka, Silica gel 60, particle size 35–70 μm). Medium performance liquid chromatography (MPLC) was performed on a Büchi Flash Chromatography System (Büchi Fraction Collector C-660, Büchi Pump Module C-605, Büchi Control Unit C-620) on silica gel (LiChroprep® Si 60, 15–25 μm), column dimensions: 23 × 460 mm, backpressure: 10 Bar, detection: UV (254 nm). Catalytic hydrogenation was performed on a Parr Pressure Reaction Hydrogenation apparatus (500 mL). Optical rotation of chiral nonracemic compounds was measured on a Perkin-Elmer 241MC polarimeter.

N-Boc-Glycine (**1a**), *N*-Cbz-glycine (**1b**), *N*-Cbz-sarcosine (**1c**), *N*-benzyl-*N*-Cbz-glycine (**1d**), CDI, potassium monomethyl malonate, anhydrous magnesium chloride, sodium borohydride, mesyl chloride, *tert*-butyl 2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**6**), glyoxal, dimethoxyacetaldehyde, sodium cyanoborohydride, sodium triacetoxyborohydride, tetrabutylammonium borohydride, trifluoroacetic acid (TFA), methyl glycinate hydrochloride (**18a**), methyl *β*-alaninate (**18b**), 2-phenylethylamine (**18c**), diethylamine (**18d**), (*S*)-*N*-Boc-alaninate (**18e**), and (*S*)-*N*-Boc-prolinate (**18f**) are commercially available. Methyl 4-*tert*-butoxycarbonylamino-3-oxobutanoate (**2a**),[40] methyl 4-benzyloxycarbonylamino-3-oxobutanoate (**2b**),[42] and 5-oxo-1-phenylpyrazolidine-3-carboxylic acid (**17**)[41] were prepared following the literature procedures.

3. 2. General Procedure for the Synthesis of *N*-protected 5-aminomethyl-3-pyrazolidinones 5a, 5b, and 5'b

Method A. Compounds **5a**, **5b**, and **5'b** were prepared in a one-pot procedure following the combined slightly modified general literature procedures for the preparation of analogous compounds.[35,38,39]

3. 2. 1. Methyl 4-*tert*-butoxycarbonylamino-3-oxobutanoate (2a)[42]

Under argon, CDI (1.94 g, 12 mmol) was added to a solution of Boc-glycine (**1a**) (1.75 g, 10 mmol) in anh. THF (20 mL) and the mixture was stirred at room temperature for 2 h. Then a solid mixture of anh. $MgCl_2$ (0.893 g, 9.5 mmol) and potassium mono-methyl malonate (2.184 g, 14 mmol) was added under Ar in one portion via a powder funnel, which was rinsed with anh. THF (5 mL) and the mixture was stirred under Ar at r.t. for 20 h. Volatile components were evaporated *in vacuo* and the residue was triturated with EtOAc (80 mL). The resulting suspension was washed with 1 M aq. $NaHSO_4$ (2 × 20 mL) and brine (20 mL). The organic phase was dried over anh. Na_2SO_4, filtered, and the filtrate was evaporated *in vacuo* to give **2a**, which was used in the next step without purification. Yield: 2.15 g (93%) of yellow oil. Spectral data were in agreement with the literature data.[42]

3. 2. 2. Methyl 4-*tert*-butoxycarbonylamino-3-hydroxybutanoate (3a)[43]

Finely powdered $NaBH_4$ (650 mg, 17.2 mmol) was slowly added to a cooled (0 °C) stirred solution of *β*-keto ester **2a** (6.94 g, 30 mmol) in MeOH (100 mL) and the resulting mixture was stirred at 0 °C for 1 h and then quenched at 0 °C by the addition of H_2O (150 mL) followed by the addition of 1 M aq. HCl (30 mL, 30 mmol). The product was extracted with dichloromethane (3 × 150 mL) and the combined organic phase was washed with brine (150 mL). The organic phase was dried over anh. Na_2SO_4, filtered, and the filtrate was evaporated *in vacuo*.

The residue was dissolved in anh. toluene (30 mL) and the solution was evaporated *in vacuo* at 40 °C/2 mbar to give anhydrous crude **3a**, which was used in the next step without further purification. Yield: 5.93 g (84%) of yellowish oil. Spectral data were consistent with the literature data.[43]

3. 2. 3. Methyl 4-*tert*-butoxycarbonylamino-3-mesyloxybutanoate (4a)

MsCl (2.25 ml, 29 mmol) was added to a cooled (0 °C) solution of *β*-hydroxy ester **3** (5.83 g, 25 mmol) in anh. pyridine (30 mL) and the resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. The reaction mixture was poured into cooled (0 °C) toluene (350mL) and the toluene solution was washed thoroughly with 1 M aq. HCl (200 mL) and brine (2 × 200mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated *in vacuo* to give crude **4a**, which was used in the next step without purification. Yield: 6.58 g (84%) of yellowish oil. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.37 (*s*, *t*-Bu); 2.20 (*dd*, *J* = 9.0; 15.1 Hz, 1H of CH_2); 2.44 (*dd*, *J* = 3.8; 15.1 Hz, 1H of CH_2); 2.86–2.98 (*m*, CH_2); 3.82–3.90 (*m*, CH); 4.94 (*d*, *J* = 5.6 Hz, OH); 6.77 (*t*, *J* = 5.8 Hz, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): *δ* 28.2, 37.0, 37.9, 43.0, 51.7, 77.4, 78.2, 155.8, 169.8.

3. 2. 4. Preparation of 3-pyrazolidinones 5a, 5b, and 5'b

Method A. Hydrazine monohydrate (0.75 mL, 15 mmol) or methylhydrazine (789 μ, 15 mmol) was added to a solution of the mesylate **4a** (3 mmol) in CH_2Cl_2 (25 mL) and the mixture was stirred at room temperature for 24–72 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC. First, the non-polar impurities and starting material **4a** were eluted (EtOAc–hexane, 1:1), followed by elution of the products **5** and **5'** (EtOAc–MeOH, 10:1). Fractions containing the product were combined and volatile components evaporated *in vacuo* to give **5a** or **5b**/**5'b**. A mixture of regioisomers **5b** and **5'b** was separated by MPLC (EtOAc–MeOH, 20:1). Fractions containing the products were combined and volatile components were evaporated *in vacuo* to give **5b** and **5'b**, respectively.

***tert*-Butyl [(5-oxopyrazolidin-3-yl)methyl]carbamate (5a)**

Prepared from **4a** (1.87 g, 6 mmol) and hydrazine hydrate (685 μL, 13.8 mmol), stirring for 24 h. Yield: 1.12 g (86%) of white solid; m.p. 103–110 °C. ^{1}H-NMR (500 MHz, DMSO-d_6): *δ* 1.38 (9H, s, *t*-Bu), 2.00 (1H, dd, *J* = 4.9; 16.4 Hz, 4-Ha), 2.36 (1H, dd, *J* = 7.9; 16.1 Hz, 4-Hb), 2.88–3.06 (2H, m, 3'-CH_2), 3.48 (1H, br s, 3-H), 5.29 (1H, br s, 2-H), 6.88 (1H, t, *J* = 5.8 Hz, N<u>H</u>CH_2), 8.98 (1H, s, 1-H). ^{13}C-NMR (126 MHz, DMSO-d_6): *δ* 28.2, 35.0, 42.4, 56.4, 77.8, 155.9, 175.0. *m*/*z* (ESI) = 216 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_9H_{18}N_3O_3$, 216.1343; found, 216.1339. Anal. Calcd for $C_9H_{17}N_3O_3$: C 50.22, H 7.96, N 19.52. Found: C 50.09, H 8.09, N 19.13. IR (ATR) ν 3344, 2970, 1692, 1649, 1522, 1445, 1392, 1365, 1277, 1252, 1175, 1124, 1081, 1053, 1000, 964, 901, 874, 782, 732, 638 cm^{-1}.

***Tert*-Butyl [(2-methyl-5-oxopyrazolidin-3-yl)methyl] carbamate (5b) and tert-butyl [(1-methyl-5-oxopyrazolidin-3-yl)methyl]carbamate (5'b).**

Prepared from **4a** (1.38 g, 4.43 mmol) and methylhydrazine (557 μL, 10.37 mmol), stirring for 72 h.

tert-*Butyl [(2-methyl-5-oxopyrazolidin-3-yl)methyl]carbamate (5b).*

Yield: 670 mg (66%) of yellow oil. ^{1}H-NMR (500 MHz, DMSO-d_6): *δ* 1.38 (9H, *s*, *t*-Bu), 1.95 (1H, dd, *J* = 4.2, 16.8 Hz, 4-Ha), 2.46 (3H, s, 2-Me), 2.70 (1H, dd, *J* = 8.1, 16.7 Hz, 4-Hb), 2.82–2.90 (1H, m, 3'-Ha), 2.99–3.08 (2H, m, 3'-Hb and 3-H), 6.89 (1H, t, *J* = 5.3 Hz, N<u>H</u>CH_2), 9.30 (1H, *s*, 1-H). ^{13}C-NMR (126 MHz, DMSO-d_6): *δ* 28.2, 32.5, 42.7, 46.6, 63.5, 77.8, 155.8, 172.1. *m*/*z* (ESI) = 230 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{10}H_{20}N_3O_3$, 230.1499; found, 230.1496. IR (ATR) *ν* 3301, 2975, 2931, 1692, 1520, 1455, 1392, 1366, 1278, 1253, 1168, 1094, 1044 cm^{-1}.

tert-*Butyl [(1-methyl-5-oxopyrazolidin-3-yl)methyl]carbamate (5'b).*

Yield: 150 mg (14%) of yellow oil. ^{1}H-NMR (500 MHz, DMSO-d_6): *δ* 1.38 (9H, s, *t*-Bu), 2.09 (1H, dd, *J* = 5.1, 16.3 Hz, 4-Ha), 2.45 (1H, dd, *J* = 8.2, 16.2 Hz, 4-Hb), 2.81 (3H, s, 1-Me), 2.86–2.94 (1H, m 3'-Ha); 2.96–3.03 (1H, m, 3'-Ha), 3.41 (1H, br *s*, 3-H), 5.67 (1H, br s, 2-H), 6.89 (1H, t, *J* = 5.8 Hz, N<u>H</u>CH_2). ^{13}C-NMR (126 MHz, DMSO-d_6): *δ* 28.2, 30.6, 35.2, 42.6, 53.0, 77.8, 155.8, 170.5. *m*/*z* (ESI) = 230 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{10}H_{20}N_3O_3$, 230.1499; found, 230.1503. IR (ATR) ν 3332, 2977, 2933, 1694, 1520, 1455, 1394, 1367, 1277, 1253, 1169, 1060, 957 cm^{-1}.

Method B. Hydrazine hydrate (729 μL, 15 mmol) was added to a solution of **6** (0.916 g, 5 mmol) in methanol (15 mL) and the mixture was stirred at r.t. for 48 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC (EtOAc–MeOH, 10:1). Fractions containing the products were combined and volatile components were evaporated *in vacuo* to give **5a**. Yield: 481 mg (45%) of a yellow resin. Characterisation data for **5a** are given above in Section 3.2.4.1.

3. 3. General Procedure for Acidolytic Deprotection of Compounds 5a, 5b, and 5'b. Synthesis of Free Amines 7–9

2 M HCl in ethyl acetate (10 mL, 20 mmol) was added to a stirred solution of **5a**, **5b**, or **5'b** (4 mmol) in methanol (20 mL) and the mixture was stirred at r.t. for 72 h.

The precipitate was collected by filtration, washed with anh. Et_2O (50 mL) and dried *in vacuo* to give **7**–**9**.

3. 3. 1. 2-(1-Ammonio-4-methoxy-4-oxobutan-2-yl)hydrazin-1-ium chloride (7)

Prepared from **5a** (861 mg, 4 mmol). Yield: 778 mg (88%) of white solid; mp 187–191 °C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.75 (1H, dd, J = 6.9, 17.0 Hz, 3-Ha), 2.83 (1H, dd, J = 6.3, 17.0 Hz, 3-Hb), 3.06 (2H, br s, 1-CH_2); 3.64 (4H, br s, CO_2Me, 2-H), 5.75 (1H, br s, NH), 8.34 (3H, br s, NH_3^+), 9.65 (3H, br s, NH_3^+). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 34.7, 39.3, 51.8, 52.8, 170.9. Anal. Calcd for $C_5H_{15}Cl_2N_3O_2$: C 27.28, H 6.87, N 19.09. Found: C 27.58, H 6.69, N 18.84. IR (ATR) ν 3437, 3198, 2987, 1727, 1598, 1523, 1471, 1442, 1376, 1301, 1232, 1189, 1054, 1000, 987, 942, 902, 869, 772 cm^{-1}.

3. 3. 2. 5-(Ammoniomethyl)-1-methyl-3-oxopyrazolidin-1-ium chloride (8)

Prepared from **5b** (688 mg, 3 mmol). Yield: 250 mg (41%) of white solid; mp 170–183 °C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.42 (1H, br d, J = 11.4 Hz, 4-Ha), 2.81 (3H, s, 1-Me), 2.98 (1H, br d, J = 13.3 Hz, 4-Hb), 3.09 (2H, br d, 3'-CH_2), 3.89 (1H, br s, 3-H), 7.90 (2H, br s, 2-H and NH^+), 8.50 (3H, br s, NH_3^+). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 32.6, 39.2, 45.2, 62.3, 171.5. m/z (ESI) = 130 (MH^+). HRMS–ESI (m/z): [MH^+] calcd for $C_5H_{12}N_3O$, 130.0975; found, 130.0974. IR (ATR) ν 3438, 3004, 2484, 1750, 1493, 1456, 1443, 1425, 1385, 1322, 1302, 1261, 1223, 1166, 1118, 1104, 1053, 1013, 919 cm^{-1}.

3. 3. 3. 5-(Ammoniomethyl)-2-methyl-3-oxopyrazolidin-1-ium chloride (9)

Prepared from **5'e** (85 mg, 0.37 mmol). Yield: 60 mg (80%) of very hygroscopic white semi-solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.40 (1H, dd, J = 4.7, 16.8 Hz, 4-Ha), 2.75 (1H, dd, J = 8.7, 16.8 Hz, 4-Hb), 2.94 (3H, s, 2-Me), 2.97–3.07 (2H, m, 5'-CH_2), 3.92–4.01 (1H, m, 5-H), 4.91 (2H, br s, NH_2^+), 8.33 (3H, br s, NH_3^+). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 30.7, 33.9, 39.9, 51.2, 169.9. m/z (ESI) = 130 (MH^+). HRMS–ESI (m/z): [MH^+] calcd for $C_5H_{12}N_3O$, 130.0975; found, 130.0972.

3. 4. *Tert*-Butyl ((2-(2,2-dimethoxyethyl)-5-oxopyrazolidin-3-yl)methyl)carbamate (11a)

$NaBH_3CN$ (465 mg, 15 mmol) was added in small portions within 1 h to a stirred solution of **5** (3.23 g, 15 mmol) and dimethoxyacetaldehyde (50% in H_2O, 4.5 mL, 30 mmol) in methanol (30 mL) and the mixture was stirred at r.t. for 48 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC (EtOAc–MeOH, 10:1). Fractions containing the product were combined and evaporated *in vacuo* to give **7a**. Yield: 1.606 g (37%) of white foam. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.37 (9H, s, t-Bu), 1.89 (1H, dd, J = 2.3, 16.4 Hz, 4'-Ha), 2.70 (1H, dd, J = 4.5, 12.7 Hz, 1H of NCH_2), 2.75 (1H, dd, J = 8.4, 16.8 Hz, 4'-Hb), 2.78–2.87 (1H, m, 1H of NCH_2), 2.89 (1H, dd, J = 5.9, 12.7 Hz, 1H of NCH_2), 3.00 (1H, m, 1H of NCH_2), 3.25 and 3.26 (6H, 2s, 1:1, 2 × OMe), 3.23–3.29 (1H, m, 3'-H overlapped by the signal for H_2O), 4.40 (1H, dd, J = 4.5, 5.9 Hz, $CH(OMe)_2$), 6.82 (1H, t, J = 5.9 Hz, $NHCH_2$), 9.34 (1H, s, 1'-H). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 28.2, 31.8, 43.0, 52.9, 53.2, 60.8, 61.9, 77.7, 101.8, 155.7, 172.2. m/z (ESI) = 304 (MH^+). HRMS–ESI (m/z): [MH^+] calcd for $C_{13}H_{25}N_3O_5$, 304.1867; found, 304.1866. IR (ATR) ν 3395, 3055, 2982, 2936, 2836, 2360, 2340, 1699, 1507, 1452, 1423, 1392, 1367, 1266, 1169, 1132, 1074, 974, 896, 866, 741, 705, 668 cm^{-1}.

3. 5. Benzyl ((2-(2,2-dimethoxyethyl)-5-oxopyrazolidin-3-yl)methyl)carbamate (11b)

The crude pyrazolidinone **5b** was prepared in four steps from *N*-Cbz-glycine (**1b**) following a one-pot procedure for the preparation of its *N*-Boc analogue **5a** (*cf.* Section 3.2. and Scheme 1). Reductive alkylation of the intermediate pyrazolidinone **5b** (1.246 g, 5 mmol) was performed in the same way as described above for the preparation of **11a**. The crude product **11b** was additionally purified by MPLC (EtOAc–MeOH, 10:1). Yield: 700 mg (41%) of yellow oil. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.91 (1H, dd, J = 2.5, 16.9 Hz, 4'-Ha), 2.71 (1H, dd, J = 4.5, 12.8 Hz, 1H of NCH_2), 2.78 (1H, dd, J = 8.3, 16.8 Hz, 4'-Hb), 2.89 (1H, dd, J = 3.2, 5.9 Hz, 1H of NCH_2), 2.90 (1H, m, 1H of NCH_2), 3.08 (1H, m, 1H of NCH_2), 3.24 and 3.25 (6H, 2s, 1:1, 2 × OMe), 3.29–3.36 (1H, m, 3'-H), 4.40 (1H, dd, J = 4.5, 5.9 Hz, $CH(OMe)_2$), 5.02 (2H, d, J = 4.3 Hz, $PhCH_2$), 7.29–7.39 (6H, m, Ph and $NHCH_2$), 9.36 (1H, s, 1'-H). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 31.8, 43.4, 53.0, 53.1, 60.8, 61.8, 65.3, 101.8, 127.7, 127.8, 128.3, 137.1, 156.3, 172.9. m/z (ESI) = 338 (MH^+). HRMS–ESI (m/z): [MH^+] calcd for $C_{16}H_{23}N_3O_5$, 338.1711; found, 338.1709. IR (ATR) ν 3336, 3058, 2938, 2836, 2360, 2342, 1698, 1519, 1455, 1266, 1134, 1073, 977, 918, 869, 830, 739, 701, 668 cm^{-1}.

3. 6. General Procedure for the Synthesis of 5-alkyl-1-methyltetrahydro-1*H*-imidazo[1,5–*b*]pyrazole-2,6-diones 14a,b

Bicyclic compounds **14a** and **14b** were obtained in nine steps from *N*-Cbz-sarcosine (**1c**) and *N*-benzyl-*N*-Cbz-glycine (**1d**). First, 3-pyrazolidinones **5c** and **5d** were prepared following a one-pot procedure for the preparation of their *N*-Boc analogue **5a** (*cf.* Section 3.2. and Scheme 1).[35]

3. 6. 1. Preparation of the Free Diamines 12a,b

Boc_2O (2.4 g, 11 mmol) was added to a stirred solution of **5c**,**d** (9 mmol) in a mixture of dioxane (12 mL), water (25 mL), and Na_2CO_3 (1.1 g, 10 mmol) and the mixture was stirred at r.t. for 24 h. Most of the dioxane was removed by evaporation *in vacuo* at 35 °C/50 mbar. EtOAc (50 mL) and brine (25 mL) were added to the aqueous residue, the biphasic system was transferred into a separatory funnel, shaken, and the phases were separated. The organic phase was washed with brine (2 × 20 mL), dried over anh. Na_2SO_4, filtered, and the filtrate was evaporated *in vacuo*. The residue was purified by CC (EtOAc/hexane, 1:1). Fractions containing the product were combined and evaporated in vacuo. Under argon, the residue was dissolved in anh. DMF (25 mL), K_2CO_3 (691 mg, 5 mmol) and methyl iodide (934 μL, 15 mmol) were added and the mixture was stirred at r.t. for 72 h. Volatile components were evaporated *in vacuo*, EtOAc (100 mL) was added to the residue, and the mixture was washed with brine (3 × 30 mL). The organic phase was dried over anh. Na_2SO_4, filtered, and the filtrate was evaporated *in vacuo*. The residue was purified by CC (EtOAc/hexane, 1:1). Fractions containing the product were combined and evaporated *in vacuo*. The residue was dissolved in dichloromethane (20 mL), TFA (5 mL) was added and the mixture was stirred at r.t. for 24 h. Volatile components were evaporated *in vacuo*, EtOAc (150 mL) and brine (50 mL) were added, and the biphasic system was made alkaline by slow addition of solid K_2CO_3 until pH 8–9 was reached. The mixture was stirred vigorously at r.t. for 5 min and then stirring was stopped and the phases were allowed to separate. The organic phase was washed with brine (2 × 10 mL), dried over anh. Na_2SO_4, filtered, and the filtrate was evaporated *in vacuo*. The residue was purified by CC (EtOAc/MeOH, 10:1). Fractions containing the product were combined and evaporated *in vacuo* to give **12a**,**b**, which were used in the next step without further purification.

3. 6. 2. Preparation of tetrahydro-1*H*-imidazo[1,5–*b*]pyrazole-2,6-diones 14a,b

A mixture of crude **12c**,**d** (1.5 mmol), methanol (20 mL), and 10% Pd–C (80 mg) was hydrogenated under 3 bar of H_2 at room temperature for 1.5 h. The catalyst was removed by filtration through a short pad of Celite®, washed with methanol (3 × 10 mL), and the combined filtrate was evaporated *in vacuo*. The residue was dissolved in toluene (20 mL) and the solution was evaporated *in vacuo* again to give anhydrous free diamine **13a**,**b**. The crude diamine **13** (1.5 mmol) was dissolved in anh. DMF (5 mL), CDI (262 mg, 1.5 mmol) was added, and the mixture was stirred at room temperature for 12 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC (EtOAc–MeOH, 10:1). Fractions containing the product were combined an evaporated *in vacuo*. The residue (a mixture of **14** and imidazole) was dissolved in EtOAc (1 mL), 2 M HCl–Et_2O (1 mL), was added and the precipitate (imidazole hydrochloride) was removed by filtration and washed with anh. Et_2O (2 × 2 mL). The filtrate was evaporated *in vacuo* to give **14a**,**b**.

1,5-Dimethyltetrahydro-1*H*-imidazo[1,5–*b*]pyrazole-2,6-dione (14a).

Prepared from **12a** (222 mg, 1.55 mmol) and CDI (265 mg, 1.55 mmol). Yield: 110 mg (42%) of yellow oil. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.41 (1H, dd, J = 7.8, 16.0 Hz, 3'-Ha), 2.70 (1H, dd, J = 11.3, 16.4 Hz, 3'-Hb), 2.75 (3H, s, 5'-Me), 3.13 (3H, s, 1'-Me), 3.35 (1H, dd, J = 1.2, 9.7 Hz, 4'-H), 3.58 (1H, dd, J = 7.35, 9.82 Hz, 4'-H), 4.30 (1H, dtd, J = 1.20, 7.65, 7.61, 10.97 Hz, CH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 30.1, 32.3, 35.3, 47.6, 53.4, 162.6, 170.1. m/z (ESI) = 130 (MH^+). HRMS–ESI (m/z): [MH^+] calcd for $C_7H_{11}N_3O_2$, 170.0924; found, 170.0926. IR (ATR) ν 3486, 2926, 2798, 1685, 1496, 1436, 1410, 1384, 1360, 1292, 1253, 1219, 1173, 1146, 1085, 1063, 1037, 1020, 974, 926, 891, 838, 790, 737, 675 cm^{-1}.

5-Benzyl-1-methyltetrahydro-1*H*-imidazo[1,5–*b*]pyrazole-2,6-dione (14b).

Prepared from **5'c** (340 mg, 1.55 mmol) and CDI (265 mg, 1.55 mmol). Yield: 201 mg (53%) of yellow oil. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.44 (1H, dd, J = 16.2, 7.7 Hz, 3-Ha), 2.59 (1H, ddd, J = 16.3, 11.2, 1.1 Hz, 3-Hb), 3.16 (1H, dd, J = 9.8, 1.1 Hz, 4-Ha), 3.34 (3H, s, 1-Me), 3.50 (1H, dd, J = 9.7, 7.3 Hz, 4-Hb), 4.25 (1H, dtd, J = 11.3, 7.5, 1.1 Hz, 3'-H), 4.34 (1H, d, J = 14.8 Hz, 1H of C$\underline{H}_2$Ph), 4.46 (1H, d, J = 14.9 Hz, 1H of C$\underline{H}_2$Ph), 7.18–7.26 (2H, m, 2H of Ph), 7.27–7.43 (3H, m, 3H of Ph). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 32.7, 36.0, 45.4, 47.6, 54.0, 128.1, 128.1, 129.0, 135.2, 162.8, 169.6. m/z (ESI) = 246 (MH^+). HRMS–ESI (m/z): [MH^+] calcd for $C_{13}H_{16}N_3O_2$, 246.1237; found, 246.1237.

3. 7. General Procedure for the Synthesis of 5-oxopyrazolidine-3-carboxamides 19a–d

Under argon, CDI (0.892 g, 5.5 mmol) was added to a stirred suspension of carboxylic acid **17** (1.031 g, 5 mmol) in anh. acetonitrile (20 mL), the mixture was stirred at r.t. for 1.5 h, followed by addition of amine **18** (5 mmol). When amine **18** hydrochloride was used, one equivalent of *N*-methylmorpholine (NMM, 600 μL, 5 mmol) was added as well. The mixture was stirred at r.t. for 12 h and volatile components were evaporated *in vacuo*. The residue was taken up in dichloromethane (30 mL) and the solution was washed with 1 M aq. $NaHSO_4$ (2 × 20 mL), saturated aq. $NaHCO_3$ (2 × 20 mL), and brine (2 × 20 mL). The organic phase was dried over anh. Na_2SO_4, filtered, and the filtrate was evaporated *in vacuo*. Volatile components were evaporated *in vacuo* and the residue was purified by CC (EtOAc). Fractions containing the product were combined an evaporated *in vacuo* to give **19a–d**.

3. 7. 1. Methyl *rac*-(5-oxo-1-phenylpyrazolidine-3-carbonyl)glycinate (19a)

Prepared from **17** (1.031 g, 5 mmol), CDI (0.892 g, 5.5 mmol), methyl glycinate hydrochloride (**18a**) (628 mg, 5 mmol), and NMM (600 μL, 5 mmol). Yield: 653 mg (45%) of red crystals; m.p. 148–152 °C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.79 (1H, dd, J = 1.3, 16.6 Hz, 4'-Ha), 3.06 (1H, dd, J = 9.3, 16.6 Hz, 4'-Hb), 3.60 (3H, s, OMe), 3.85–3.97 (2H, m, C$\underline{H}_2$CO$_2$Me), 4.16–4.22 (1H, m, 5'-H), 6.86 (1H, d, J = 6.8 Hz, 1'-H), 7.12 (1H, t, J = 7.4 Hz, 1H of Ph), 7.37 (2H, dd, J = 7.3, 8.6 Hz, 2H of Ph), 7.86 (2H, td, J = 1.2, 7.5 Hz, 2H of Ph), 8.57 (1H, t, J = 6.1 Hz, N$\underline{H}$CH$_2$). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 36.8, 40.7, 51.7, 54.6, 118.1, 123.7, 128.4, 138.8, 169.8, 170.0, 171.2. m/z (ESI) = 278 (MH$^+$). HRMS–ESI (m/z): [MH$^+$] calcd for $C_{13}H_{15}N_3O_4$, 278.1135; found, 278.1138. Anal. Calcd for $C_{13}H_{15}N_3O_4$: C 56.31, H 5.45, N 15.15. Found: C 56.05, H 5.53, N 14.87. IR (ATR) ν 3359, 3219, 3005, 2959, 2930, 1754, 1695, 1655, 1593, 1525, 1489, 1461, 1440, 1403, 1358, 1338, 1312, 1281, 1242, 1205, 1160, 1127, 1096, 1075, 1031, 1013, 983, 968, 956, 932, 909, 828, 764, 718, 692, 659, 617 cm^{-1}.

3. 7. 2. Methyl *rac*-3-(5-oxo-1-phenylpyrazolidine-3-carboxamido)propanoate (19b)

Prepared from **17** (208 mg, 1 mmol), CDI (178 mg, 1.1 mmol), methyl β-alaninate hydrochloride (**18b**) (140 mg, 1 mmol), and NMM (120 μL, 1 mmol). Yield: 131 mg (45%) of pale yellowish crystals; m.p. 88–91 °C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.41–2.54 (2H, m, C$\underline{H}_2$NH), 3.07 (1H, dd, J = 17.2, 9.3 Hz, 4'-Ha), 3.13 (1H, dd, J = 17.2, 3.5 Hz, 4'-Hb), 3.47 (1H, ddt, J = 13.6, 7.3, 5.1 Hz, C$\underline{H}_2$CO$_2$Me), 3.50–3.60 (4H, m, O$\underline{Me}$ and 1H of C$\underline{H}_2$CO$_2$Me), 4.09 (1H, ddd, J = 9.7, 6.6, 3.4 Hz, 5'-H), 5.43 (1H, d, J = 6.6 Hz, 1'-H), 7.14 (1H, t, J = 7.4 Hz, 1H of Ph), 7.37 (2H, dd, J = 8.7, 7.3 Hz, 2H of Ph), 7.78 (1H, s, N$\underline{H}$CO), 7.82 (2H, d, J = 7.6 Hz, 2H of Ph). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 33.7, 34.8, 37.2, 51.8, 55.31, 118.0, 124.7, 128.9, 138.2, 169.5, 170.0, 172.6. m/z (ESI) = 292 (MH$^+$). HRMS–ESI (m/z): [MH$^+$] calcd for $C_{14}H_{17}N_3O_4$, 292.1292; found, 292.1295. Anal. Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.89; H, 5.61; N, 14.20. IR (ATR) ν 3371, 3284, 3073, 3026, 2954, 2932, 2883, 2848, 1722, 1695, 1593, 1525, 1496, 1455, 1434, 1398, 1361, 1337, 1323, 1309, 1272, 1231, 1198, 1178, 1160, 1121, 1078, 1054, 1028, 1009, 967, 925, 894, 875, 817, 753, 713, 690, 667, 615 cm^{-1}.

3. 7. 3. 5-Oxo-*N*-phenethyl-1-phenylpyrazolidine-3-carboxamide (19c)

Prepared from **17** (208 mg, 1 mmol), CDI (178 mg, 1.1 mmol), and 3-phenylethylamine (**18c**) (126 μL, 1 mmol). Yield: 154 mg (50%) of white crystals; m.p. 131–133 °C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.73 (2H, td, J = 4.5, 6.7, 6.9 Hz, NHC$\underline{H}_2$), 3.02 (1H, dd, J = 9.6, 17.7 Hz, 4'-Ha), 3.09 (1H, dd, J = 3.3, 17.3 Hz, 4'-Hb), 3.45 (1H, qd, J = 6.4, 13.1 Hz, 1H of C$\underline{H}_2$Ph), 3.58 (1H, qd, J = 6.5, 13.1 Hz, 1H of C$\underline{H}_2$Ph), 4.02 (1H, ddd, J = 3.3, 6.6, 9.8 Hz, 5'-H), 5.31 (1H, d, J = 6.7 Hz, 1'-H), 7.01–7.08 (1H, m, 1H of Ph), 7.11–7.24 (5H, m, Ph), 7.30–7.38 (2H, m, 2H of Ph), 7.67 (2H, d, J = 7.8 Hz, 2H of Ph). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 35.4, 37.3, 40.4, 55.2, 117.8, 124.7, 126.6, 128.6, 128.7, 129.0, 138.2, 138.3, 169.4, 169.9. m/z (ESI) = 310 (MH$^+$). HRMS–ESI (m/z): [MH$^+$] calcd for $C_{18}H_{20}N_3O_2$, 310.1550; found, 310.1555. Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.78; H, 6.13; N, 13.53. IR (ATR) ν 3314, 3193, 3079, 3061, 3024, 2936, 2863, 1944, 1872, 1805, 1686, 1651, 1593, 1539, 1492, 1479, 1454, 1434, 1361, 1323, 1311, 1298, 1287, 1252, 1217, 1189, 1153, 1120, 1087, 1065, 1031, 1004, 982, 952, 932, 902, 868, 833, 747, 716, 688, 657, 614 cm^{-1}.

3. 7. 4. *N*,N-Diethyl-5-oxo-1-phenylpyrazolidine-3-carboxamide (19d)

Prepared from **17** (208 mg, 1 mmol), CDI (178 mg, 1.1 mmol), and diethylamine (**18d**) (104 μL, 1 mmol). Yield: 128 mg (49%) of pale greyish crystals; m.p. 77–79 °C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.05 (3H, t, J = 7.1 Hz, Me), 1.18 (3H, t, J = 7.0 Hz, Me), 2.85 (2H, d, J = 15.7 Hz, 4'-CH$_2$), 3.32 (2H, m, C$\underline{H}_2$Me), 3.42 (2H, m, C$\underline{H}_2$Me), 4.55 (1H, m, 5'-H), 6.39 (1H, d, J = 9.37 Hz, 1'-H), 7.07 (1H, t, J =7.4 Hz, 1H of Ph), 7.33 (2H, t, J = 7.85 Hz, 2H of Ph), 7.77 (2H, d, J = 8.10 Hz, 2H of Ph). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 12.7, 14.4, 37.4, 39.6, 40.9, 53.2, 117.7, 123.4, 128.4, 139.1, 168.2, 170.5. m/z (ESI) = 262 (MH$^+$). HRMS–ESI (m/z): [MH$^+$] calcd for $C_{14}H_{20}N_3O_2$, 262.1550; found, 262.1551. Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.44; H, 7.20; N, 15.93. IR (ATR) ν 3212, 3063, 2979, 2932, 2901, 2873, 2159, 1699, 1631, 1593, 1496, 1481, 1471, 1424, 1369, 1320, 1272, 1233, 1218, 1154, 1140, 1102, 1072, 1042, 1029, 997, 965, 938, 906, 878, 843, 815, 760, 720, 692, 671, 660 cm^{-1}.

3. 8. General Procedure for the Synthesis of Non-racemic Carboxamides 19e,f and 19'e,f

Mixtures of diastereomeric carboxamides **19e/19'e** and **19e/19'f** were prepared from racemic carboxylic acid **17** and (*S*)-amino esters **18e** and **18f**, respectively, following the general procedure for the preparation of racemic carboxamides **19a**–**d**. Mixtures of diastereomers **19e/19'e** and **19f/19'f** were separated by MPLC (EtOAc–hexane). Fraction containing the products were combined and evaporated *in vacuo* to give the non-racemic diastereomerically pure carboxamides **19e**, **19'e**, **19f**, and **19'f**.

3. 8. 1. Methyl (5*R*,2'*S*)-(3-oxo-2-phenylpyrazolidine-5-carbonyl)alaninate (19e) and its (5*S*,2'*S*)-isomer 19'e

Prepared from **17** (0.208 g, 1 mmol), CDI (0.178 g, 1.1 mmol), methyl (*S*)-alaninate hydrochloride (**18e**) (140

mg, 1 mmol), and NMM (120 μL, 1 mmol); MPLC (EtOAc–hexane, 1:1).

*Data for the (–)-isomer **19e**.* Yield: 67 mg (23%) of yellow oil; $[\alpha]_D^{22}$ –64.5 (*c* 0.365, CH_2Cl_2), MPLC: R_t = 67 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (3H, d, *J* = 7.2 Hz, Me), 3.13 (2H, d, *J* = 6.4 Hz, 4'-CH_2), 3.75 (3H, s, CO_2Me), 4.16 (1H, q, *J* = 6.6 Hz, 2-H), 4.54 (1H, m, 5'-H), 5.48 (1H, d, *J* = 6.7 Hz, 3-H), 7.16 (1H, t, *J* = 7.4 Hz, 1H of Ph), 7.38 (2H, dd, *J* = 7.4, 8.7 Hz, 2H of Ph), 7.73 (1H, s, 1'-H), 7.83 (2H, dd, *J* = 1.2, 8.8 Hz, 2H of Ph). ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.25, 37.22, 48.06, 52.63, 55.29, 117.97, 124.84, 129.04, 138.23, 169.39, 169.80, 173.12. *m*/*z* (ESI) = 292 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{14}H_{17}N_3O_4$, 292.1292; found, 292.1292. IR (ATR) ν 3469, 3367, 3227, 3068, 2992, 2952, 2848, 1739, 1664, 1595, 1518, 1495, 1454, 1352, 1323, 1310, 1210, 1154, 1112, 1056, 1030, 979, 932, 894, 847, 827, 754, 691, 670, 629 cm^{-1}.

*Data for the (+)–isomer **19'e**.* Yield: 60 mg (21%) of yellow oil; $[\alpha]_D^{22}$ +82.2 (*c* 0.39, CH_2Cl_2), MPLC: R_t = 78 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (3H, d, *J* = 7.1 Hz, Me), 3.09 (1H, dd, *J* = 9.3, 17.2 Hz, 4'-Ha), 3.16 (1H, dd, *J* = 3.5, 17.2 Hz, 4'-Hb), 3.62 (3H, s, CO_2Me), 4.14 (1H, ddd, *J* = 3.5, 6.6, 9.7 Hz, 2-H), 4.54 (1H, m, 5'-H), 5.44 (1H, d, *J* = 6.7 Hz, 3-H), 7.16 (1H, t, *J* = 7.4 Hz, 1H of Ph), 7.38 (2H, dd, *J* = 7.4, 8.7 Hz, 1H of Ph), 7.81–7.90 (3H, m, 1'-H and 2H of Ph). ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.4, 37.0, 48.2, 52.5, 55.4, 118.42, 124.9, 129.0, 138.2, 169.3, 169.6, 172.6. *m*/*z* (ESI) = 292 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{14}H_{17}N_3O_4$, 292.1292; found, 292.1293. IR (ATR) ν 3486, 3369, 3226, 3066, 2992, 2952, 2848, 1739, 1665, 1595, 1518, 1495, 1453, 1353, 1325, 1310, 1211, 1154, 1110, 1061, 1030, 1019, 980, 933, 899, 846, 827, 754, 691, 670, 617 cm^{-1}.

3. 8. 2. Methyl (5*R*,2'*S*)-(3-oxo-2-phenylpyrazolidine-5-carbonyl)prolinate (19f) and its (5*S*,2'*S*)-isomer 19'f

Prepared from **17** (0.208 g, 1 mmol), CDI (0.178 g, 1.1 mmol), methyl (*S*)-prolinate hydrochloride (**18f**) (166 mg, 1 mmol), and NMM (120 μL, 1 mmol); MPLC (EtOAc–hexane, 2:1).

*Data for the (–)-isomer **19f**.* Yield: 40 mg (13%) of yellow oil; $[\alpha]_D^{22}$ –98.1 (*c* 0.425, CH_2Cl_2), MPLC: R_t = 67 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.03–2.10 (2H, m, 4'-CH_2), 2.09–2.18 (1H, m, 3-CH_2), 2.23–2.31 (1H, m, 3-CH_2), 2.95 (1H, dd, *J* = 8.2, 16.5 Hz, 4'-CH_2), 3.07 (1H, dd, *J* = 11.3, 16.5 Hz, 4'-CH_2), 3.54–3.63 (1H, m, 5-CH_2), 3.65–3.71 (1H, m, 5-CH_2), 3.76 (3H, s, CO_2Me), 4.51 (1H, dt, *J* = 8.2, 11.0 Hz, 5-H), 4.60 (1H, dd, *J* = 3.9, 8.8 Hz, 2'-H), 5.67 (1H, d, *J* = 10.8 Hz, NH), 7.13 (1H, t, *J* = 7.4 Hz, 1H of Ph), 7.36 (2H, dd, *J* = 7.3, 8.7 Hz, 2H of Ph), 7.84 (2H, d, *J* = 7.3 Hz, 2H of Ph). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.7, 28.8, 37.5, 46.4, 52.5, 54.9, 59.0, 118.4, 124.5, 128.7, 138.4, 168.4, 168.6, 172.0. *m*/*z* (ESI) = 318 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{16}H_{19}N_3O_4$, 318.1448; found, 318.1447. IR (ATR) ν 3496, 3210, 3066, 2953, 2881, 2248, 1740, 1695, 1645, 1595, 1496, 1456, 1434, 1418, 1357, 1323, 1311, 1280, 1196, 1173, 1094, 1030, 998, 984, 963, 910, 861, 834, 790, 755, 728, 691, 670, 647, 616 cm^{-1}.

*Data for the (+)–isomer **19'f**.* Yield: 43 mg (14%) of yellow oil; $[\alpha]_D^{22}$ +2.5 (*c* 0.43, CH_2Cl_2), MPLC: R_t = 84 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.02–2.13 (2H, m, 4-CH_2), 2.11–2.20 (1H, m, 3-CH_2), 2.23–2.29 (1H, m, 3-CH_2), 2.89 (1H, dd, *J* = 8.1, 16.1 Hz, 4'-CH_2), 3.02 (1H, dd, *J* = 11.3, 16.2 Hz, 4'-CH_2), 3.47 (1H, td, *J* = 7.1, 9.6, 5-CH_2), 3.76 (3H, s, CO_2Me), 3.85 (1H, ddd, *J* = 4.3, 8.0, 10.0 Hz, 5-CH_2) 4.51–4.54 (1H, m, 5-H), 4.55–4.58 (1H, m, 2'-H), 5.59 (1H, d, *J* = 10.7 Hz, NH), 7.13 (1H, t, *J* = 7.4 Hz, 1H of Ph), 7.36 (2H, dd, *J* = 7.3, 8.7 Hz, 2H of Ph), 7.86 (2H, d, *J* =7.6 Hz, 2H of Ph). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.6, 29.0, 37.6, 46.6, 52.5, 55.1, 59.2, 118.4, 124.5, 128.7, 138.4, 168.3, 168.6, 172.0. *m*/*z* (ESI) = 318 (MH^+). HRMS–ESI (*m*/*z*): [MH^+] calcd for $C_{16}H_{19}N_3O_4$, 318.1448; found, 318.1447. IR (ATR) ν 3468, 3212, 3064, 2953, 2882, 2251, 1739, 1695, 1643, 1595, 1495, 1455, 1434, 1419, 1356, 1323, 1311, 1282, 1196, 1172, 1094, 1031, 996, 981, 911, 856, 836, 792, 755, 729, 691, 670, 646, 615 cm^{-1}.

4. Conclusions

1,2-Unsubstituted 5-aminomethyl-3-pyrazolidinones are available in four steps from *N*-protected glycines and their *N*-alkylated analogues. Although the alternative one-step 'ring switching' synthesis of 5-aminomethyl-3-pyrazolidinones is definitely simpler and shorter, the high price or difficult availability of the starting *N*-protected pyrrolin-2(5*H*)-one, as well as lower yield and purity of the so obtained product are disadvantageous. Regioselective reductive alkylation 1,2-unsubstituted pyrazolidinones with dimethoxyacetaldehyde provided the 1-(2,2-dimethoxyethyl) substituted 3-pyrazolidinones, which, unfortunately could not be cyclized into the desired hexahydropyrazolo[1,5–*a*] pyrazin-2(1*H*)-ones. On the other hand, a three step selective methylation provided selectively the 2-methyl regioisomers as key-intermediates in the preparation of two novel 1,5-dialkyltetrahydro-1*H*-imidazo[1,5–*b*]pyrazole-2,6 -diones, as rare representatives of almost unexplored 3D-rich heterocyclic system. The number of synthetic steps in the above preparations may seem disadvantageous, nevertheless, this is compensated by performing up to five subsequent steps via a one-pot procedure. Amidation of easily available 3-oxopyrazolidine-5-carboxylic acid yielded the corresponding carboxamides in moderate yields. Diastereomeric non-racemic carboxamides obtained from (*S*)-AlaOMe and (*S*)-ProOMe are separable by MPLC.

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Povzetek

Študirali smo sinteztne pristope za pripravo novih 3-pirazolidinonskih derivatov funkcionaliziranih na položajih N(1) in/ali C(5). 5-aminoalkil-3-pirazolidinone smo pripravili v štirih korakih iz *N*-zaščitenih glicinov preko *Masamune-Claisenove* homologacije, redukcije, O-meziliranja in ciklizacije z derivati hidrazina. Proste amine smo pripravili z odščito v kislem. Ciljno spojino smo pripravili tudi z 'ring switching' transformacijo *N*-Boc-pirolin-2(5*H*)-ona s hidrazin hidratom. S katalitskim hidrogeniranjem smo odščitili 5-(*N*-alkil-*N*-Cbz-aminometil)pirazolidine-3-one in s sledečo ciklizacijo z 1,1'-karbonildiimidazolom (CDI) pripravili dva nova predstavnika perhidroimidazo[1,5-*b*]pirazola, ki je skoraj popolnoma neraziskan heterociklični system. Pri amidiranju 3-oksopirazolidin-5-karboksilne kisline smo dobili ustrezne karboksamide s srednjimi izkoristki. Diastereomerne neracemne karboksamide, pripravljene iz (*S*)-AlaOMe in (*S*)-ProOMe, smo ločili s pomočjo MPLC kromatografske tehnike.