A Simple Synthesis of Polyfunctionalized 4-Aminopyrazolidin-3-ones as 'Aza-deoxa' Analogs of D-Cycloserine

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A simple five-step synthesis of fully substituted (4*RS*,5*RS*)-4-aminopyrazolidin-3-ones as analogs of D-cycloserine was developed. It comprises a two-step preparation of 5-substituted (4*RS*,5*RS*)-4-(benzyloxycarbonylamino)pyrazolidin-3-ones, reductive alkylation at N(1), alkylation of the amidic N(2) with alkyl halides, and simultaneous hydrogenolytic deprotection/reductive alkylation of the primary NH_2 group. The synthesis enables an easy stepwise functionalization of the pyrazolidin-3-one core with only two types of common reagents, aldehydes (or ketones) and alkyl halides. The structures of products were elucidated by NMR spectroscopy and X-ray diffraction.

1. Introduction. – As cyclic analogs of 3-hydrazinopropanoic acid, pyrazolidin-3-ones are easily available by treatment of α,β-unsaturated carboxylic acid derivatives with $NH_2NH_2 \cdot H_2O$ [1–4]. The importance of pyrazolidin-3-one derivatives grew significantly during the last decades due to their synthetic applicability and biological activity. The most representative examples of important pyrazolidin-3-ones are phenidone (**1**) as photographic developer [5] and COX-inhibitor [6], and *Eli Lilly*'s antibiotics (**2**) [7] (*Fig. 1*). Recent applications of pyrazolidin-3-ones include their use as templates in enantioselective *Diels–Alder* [8][9], *Michael* [10][11], and 'click' reactions [12–14].

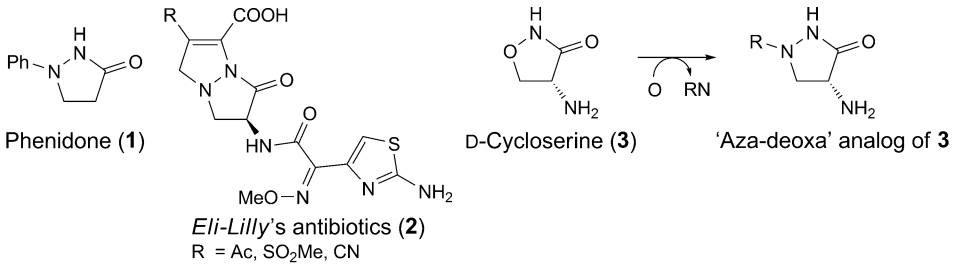


Fig. 1. *Examples of important pyrazolidin-3-ones* **1** *and* **2**, *and 4-aminopyrazolidinones, structural analogs of (*R*)-4-aminoisoxazolidin-3-one* (D-cycloserine; **3**)

D-Cycloserine (**3**; *Fig. 1*), an antibiotic effective against *Mycobacterium tuberculosis*, is applied for treatment of tuberculosis as a second-line drug, due to its adverse effects [15][16]. Recently, D-cycloserine (**3**) has also been used for cognitive behavioral therapy for anxiety disorders [17], and for treatment of behavioral and neuroinflammatory disorders in *Parkinson*'s disease [18]. Therefore, development of simple and efficient synthetic methods for preparation of novel structural analogs as well as synthesis of libraries of novel 4-aminopyrazolidin-3-one derivatives for biological screening (and other applications) seems justified.

In the last two decades, part of our research interest has also been directed to the chemistry of pyrazolidinones with focus on 1,3-dipolar cycloadditions of (1*Z*,4*R*,5*R*)-4-(benzoylamino)-1-benzylidene-3-oxopyrazolidin-1-azomethine imines to various dipolarophiles [4][13]. Within this context, reductive alkylation of (4*R*,5*R*)-4-(benzoylamino)-3-oxo-5-phenylpyrazolidine has also been reported [19]. Recently, we reported the synthesis of (4*RS*,5*RS*)-4-{[(benzyloxy)carbonyl]amino}-5-phenylpyrazolidin-3-one (**5f**) from methyl 2-{[(benzyloxy)carbonyl]amino}-2-(dimethoxyphosphoryl)acetate (**4b**) *via* the corresponding *N*-Cbz-α,β-dehydro-β-phenylalanine ester **7f** and transformations of **5f** into the hydantoin derivative [20]. The availability of *N*-deprotectable 4-aminopyrazolidinones **5** and their structural analogy with (*R*)-4-aminoisoxazolidin-3-one (D-cycloserine; **3**) prompted us to extend this study towards the synthesis of 'aza-deoxa' analogs of **3** (*Fig. 1*) with the ring O-atom, O(1), replaced by a N-atom, and with different alkyl substituents at C(5), N(1), N(2), and 4-NH_2. We herein report a simple five-step synthetic protocol for the synthesis of polyfunctionalized 4-amino-3-pyrazolidinones **5**, **10**, and **12**–**19**.

2. Results and Discussion. – The 5-unsubstituted pyrazolidinone **5a** [21] was obtained by heating methyl *N*-[(benzyloxy)carbonyl]-*O*-tosyl-L-serinate (**4a**) with excess $NH_2NH_2 \cdot H_2O$ in MeOH, as described for the synthesis of the Boc analog of **5a** [22]. Next, 3-substituted methyl 2-{[(benzyloxy)carbonyl]amino}prop-2-enoates **7b**–**7k** were prepared by *Wittig–Horner* condensation of **4b** with aldehydes and ketones **6b**–**6k** following a slightly modified procedure of *Schmidt et al.* [23]. As in previously reported successful examples [4][20][24], **7b**–**7j** were then treated with excess $NH_2NH_2 \cdot H_2O$ in an alcohol at room temperature or at reflux to afford the corresponding pyrazolidin-3-ones **5b**–**5j**, respectively, in yields between 23 and 100% (*Scheme 1* and *Table 1*).

For further transformations, the representative pyrazolidinones **5a**–**5d**, **5f**, and **5g** were used. Acid-catalyzed treatment of **5** with acetone (**6d**) and aromatic aldehydes **6f** and **6k**–**6m** in MeOH gave the corresponding azomethine imines **9a**–**9k** in yields in the range of 31–99% yield (*Scheme 2*). The deuterated compound **9k** was first obtained unintentionally. After recording the NMR spectra of **5g** in (D_6)acetone (**6m**), the solution was left to stand at room temperature for several days to give **9k** as an insoluble precipitate. In the repeated experiment, **5g** was treated with excess **6m** to furnish **9k** in 75% yield. Reduction of **9c** with $NaBH_4$ in MeOH at room temperature afforded the *N(1)*-benzyl derivative **10e** in 93% yield (*Path A*). The additional *N(1)*-alkyl derivatives **10** were prepared by an one-pot procedure *via in situ* formation of azomethine imines **9**, followed by subsequent reduction with $NaBH_4$. In this manner, a series of ten *N(1)*-alkylated 4-{[(benzyloxy)carbonyl]amino}pyrazolidin-3-ones **10**

Scheme 1

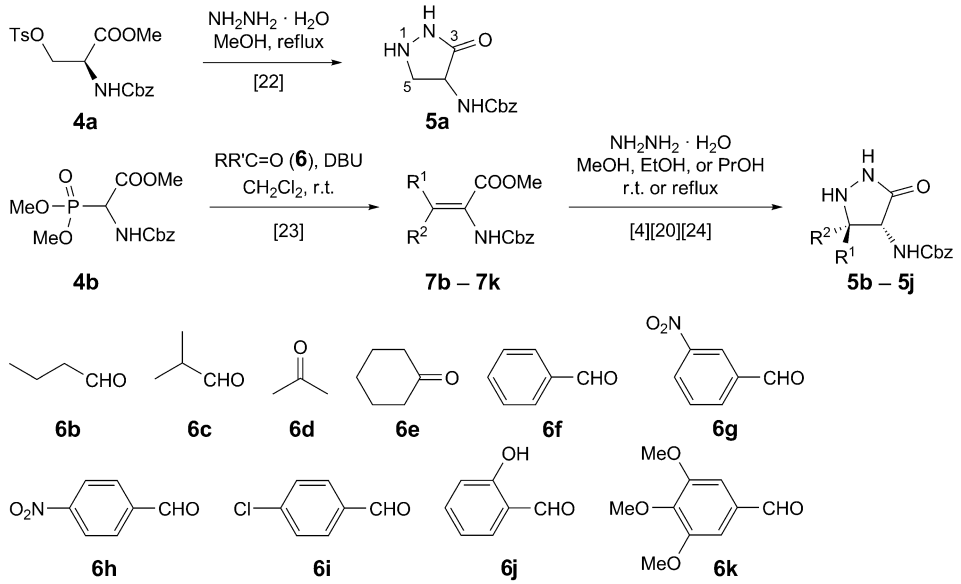


Table 1. *Yields of Compounds* **5a**–**5j**

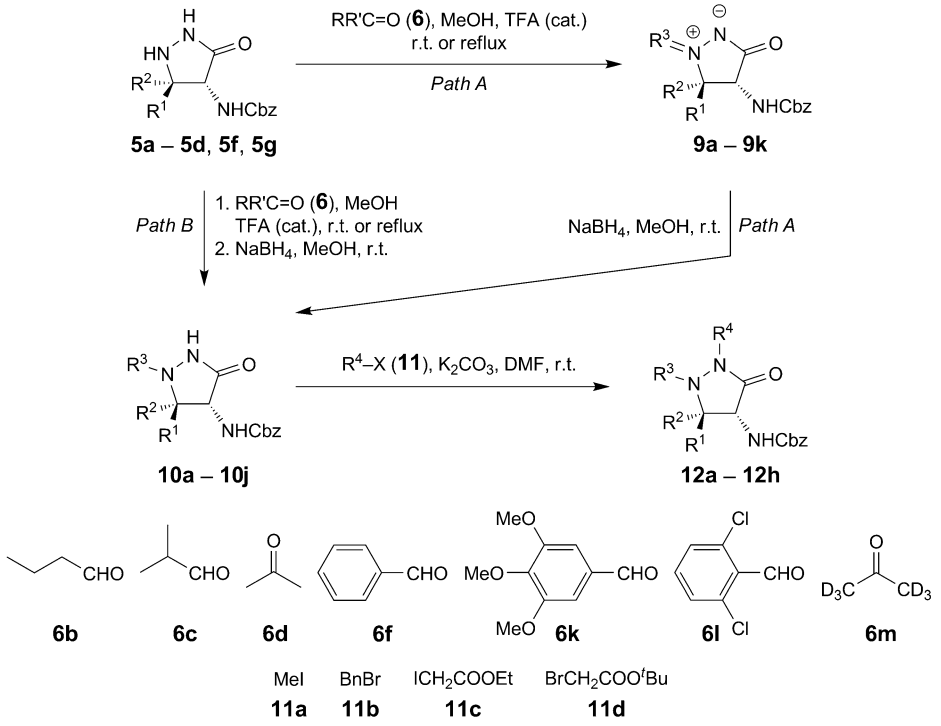
Compound	R^1	R^2	Yield [%][a])
5a	H	H	62
5b	Pr	H	45
5c	^{i}Pr	H	83 [24]
5d	Me	Me	69
5e	$-(CH_2)_5-$		23
5f	Ph	H	85 [20]
5g	3-NO_2–C_6H_4	H	44
5h	4-NO_2–C_6H_4	H	100
5i	4-Cl–C_6H_4	H	43
5j	2-HO–C_6H_4	H	49

[a]) Yields of the isolated products.

were obtained (yields, 21–95%; *Path B*). S_N2-Type alkylation at the amidic N(2)-atom was achieved with alkyl halides **11a**–**11d** in DMF in the presence of K_2CO_3 at room temperature to furnish the fully substituted 4-aminopyrazolidin-3-ones **12** (yields, 45–97%; *Scheme 2* and *Table 2*).

Finally, transformations of the [(benzyloxy)carbonyl]amino group at C(4) were studied. Hydrogenolytic deprotection of the 4-amino function in the Cbz-protected intermediates **5c**, **10d**, **10e**, **12e**, and **12h** gave the free amines **13**, **14a**, **14b**, **15a**, and **15b**, respectively, in almost quantitative yields (*Scheme 3*). When hydrogenolytic deprotection of the 1,5-disubstituted 4-{[(benzyloxy)carbonyl]amino}pyrazolidin-3-ones **10a**

Scheme 2



and **10d** was carried out in the presence of **6**, the 4-(alkylamino)pyrazolidin-3-ones **16a**–**16i** were obtained (yields, 75–100%). Somewhat surprisingly, acylations of the 1,2-unsubstituted (4*RS*,5*RS*)-4-amino-5-isopropylpyrazolidin-3-one **13** with acid chlorides or with carboxylic acids in the presence of activating reagents, such as 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ) and 1,1′-carbonyldiimidazole (CDI), did not give the desired carboxamides. The only successful *N*-acylation of **13** was the reaction with [1,1′-biphenyl]-4-carboxylic acid (**20a**) in the presence of bis(pentafluorophenyl) carbonate (BPC) in DMF, which afforded the corresponding *N*-acyl derivative **17** in 10% yield. Though surprising, the difficult acylation of the NH_2 group could be the result of the highly polar character of **13** as a cyclic α-amino hydrazide containing three different amino groups. On the other hand, acylation of the 1-substituted and, hence, less polar (4*RS*,5*RS*)-4-amino-1-benzyl-5-isopropylpyrazolidin-3-ones **14a** and **15a** with 2-phenylacetic acid (**20b**) and EEDQ in CH_2Cl_2 proceeded smoothly to furnish the corresponding carboxamides **18** and **19** in 83 and 82% yield, respectively (*Scheme 3* and *Table 3*).

The structures of all novel compounds were determined by spectroscopic methods (IR, ^{1}H- and ^{13}C-NMR, and HR-MS) and by elemental analyses for C, H, and N. Physical and spectroscopic data of known compounds **5a** [21]; **5c**, **9c**, **9d** [24]; and **9h** and **9j** [20] were in agreement with those in the literature. Compounds **5i**, **5j**, **7i**–**7k**, **9k**,

Table 2. *Yields of Compounds* **9**, **10**, *and* **12**

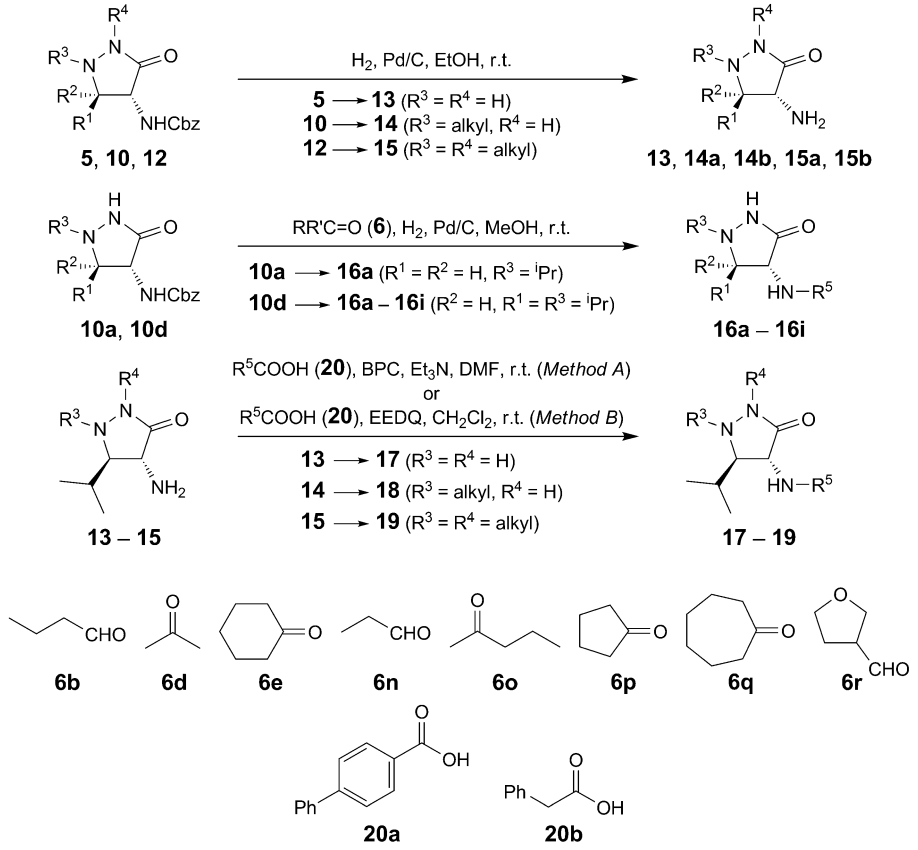
Compound	R^1	R^2	R^3	R^4	Yield [%]
9a	H	H	Benzylidene	–	31
9b	Pr	H	Benzylidene	–	58
9c	^{i}Pr	H	Benzylidene	–	96 [24]
9d	^{i}Pr	H	2,6-Dichlorobenzylidene	–	99 [24]
9e	Me	Me	Benzylidene	–	77
9f	Me	Me	2,6-Dichlorobenzylidene		60
9g	Ph	H	Isopropylidene	–	86
9h	Ph	H	Benzylidene	–	81 [20]
9i	Ph	H	3,4,5-Trimethoxybenzylidene	–	79
9j	Ph	H	2,6-Dichlorobenzylidene	–	74 [20]
9k	3-NO_2–C_6H_4	H	(D_6)Isopropylidene	–	75
10a	H	H	^{i}Pr	–	90[a])
10b	^{i}Pr	H	Bu	–	21[a])
10c	^{i}Pr	H	^{i}Bu	–	48[a])
10d	^{i}Pr	H	^{i}Pr	–	92[a])
10e	^{i}Pr	H	Bn	–	56[a]), 93[b])
10f	Me	Me	Bn	–	53[a])
10g	Ph	H	Bu	–	63[a])
10h	Ph	H	^{i}Bu	–	78[a])
10i	Ph	H	^{i}Pr	–	21[a])
10j	Ph	H	Bn	–	95
12a	^{i}Pr	H	^{i}Pr	Me	61
12b	^{i}Pr	H	^{i}Pr	Bn	45
12c	^{i}Pr	H	^{i}Pr	CH_2COOEt	76
12d	^{i}Pr	H	^{i}Pr	CH_2COO^tBu	53
12e	^{i}Pr	H	Bn	Me	70
12f	^{i}Pr	H	Bn	Bn	73
12g	^{i}Pr	H	Bn	CH_2COOEt	97
12h	Ph	H	Bn	Me	50

[a]) Obtained by a one-pot procedure from **5**. [b]) Obtained by reduction of **9c**.

10c, **10h**, **12d**, **12h**, **14a**, **14b**, **15a**, **15b**, **16a**–**16i**, and **17** were not obtained in analytically pure form. Their identities were confirmed by ^{13}C-NMR and HR-MS analyses.

The spectroscopic data of the pyrazolidinones **5**, **10**, and **12**–**19**, and azomethine imines **9** were in agreement with those in the literature reported for closely related compounds [4][19][20][24]. In solution, pyrazolidinone derivatives **5**, **9**, **10**, and **12**–**19** can equilibrate between the two envelope conformers **A** and **C** *via* the planar conformer **B** (*Fig. 2*). The conformations in solution were established by ^{1}H-NMR spectroscopy on the basis of the magnitude of the vicinal coupling constants, $^3J(4,5)$ and $^3J(1,5)$. According to the coupling constants $^3J(1,5) \approx {}^3J(4,5) \approx 11$, the 4,5-disubstituted compounds **5**, **13**, and **17** occur as envelope conformers **A** with pseudoaxial H–N(1), H–C(4), and H–C(5) (θ *ca.* 180°). In contrast, small vicinal coupling constants, $^3J(4,5) \approx 3$, in 1,2,4,5-tetrasubstituted pyrazolidinones **12**, **14**–**16**, **18**, and **19** were in agreement with conformer **C**, where H–C(4) and H–C(5) were pseudoequatorial ($\theta \sim 100°$). The conformation of 1,4,5-trisubstituted compounds **10** was dependent on the substituent at C(5): **10g**–**10j** with a Ph substituent adopted conformation **A** with

Scheme 3



pseudoaxial H–C(4) and H–C(5) ($^3J(4,5) \approx 11$ Hz), while $^3J(4,5) \approx 7$ in 5-isopropylpyrazolidinones **10b**–**10e** was in agreement with the flat conformer **B** (θ *ca.* 120°). Similarly, $^3J(4,5) \approx 5$, in dipoles **9** also supported the planar conformer **B** (*Fig. 2*).

The structures of compounds **9k**, **10f**, and **18** were determined by X-ray crystallography (*Figs. 3–5*). The conformations of compounds **9k**, **10f**, and **18** in the solid state were in agreement with the conformations in solution determined by NMR spectroscopy.

Most of the synthesized compounds were also tested for their inhibitory activities on two bacterial peptidoglycan biosynthesis enzymes, MurD ligase (MurD) and D-alanine:D-alanine ligase (DdlB) [25]. The Malachite green assay [26], which detects the orthophosphate generated during enzymatic reactions, was used. Unfortunately, none of the tested compounds inhibited these two enzymes.

3. Conclusions. – In conclusion, a simple five-step method for the synthesis of polyfunctionalized 4-aminopyrazolidin-3-ones from α-(phosphoryl)glycine ester **4b** was developed. The advantage of this method is its simplicity, which is reflected in a

Table 3. *Yields of Compounds* **13**–**19**

Compound	R^1	R^2	R^3	R^4	R^5	Yield [%]
13	^{i}Pr	H	H	H	–	100
14a	^{i}Pr	H	^{i}Pr	H	–	100
14b	^{i}Pr	H	Bn	H	–	90
15a	^{i}Pr	H	Bn	Me	–	97
15b	Ph	H	Bn	Me	–	94
16a	H	H	^{i}Pr	–	^{i}Pr	100
16b	^{i}Pr	H	^{i}Pr	–	Bu	94
16c	^{i}Pr	H	^{i}Pr	–	^{i}Pr	100
16d	^{i}Pr	H	^{i}Pr	–	Cyclohexyl	100
16e	^{i}Pr	H	^{i}Pr	–	Pr	96
16f	^{i}Pr	H	^{i}Pr	–	Pentan-2-yl	75
16g	^{i}Pr	H	^{i}Pr	–	Cyclopentyl	99
16h	^{i}Pr	H	^{i}Pr	–	Cycloheptyl	100
16i	^{i}Pr	H	^{i}Pr	–	(Tetrahydrofuran-3-yl)methyl	100
17	–	–	H	H	[1,1′-Biphenyl]-4-carbonyl	10
18	–	–	^{i}Pr	H	2-Phenylacetyl	83
19	–	–	Bn	Me	2-Phenylacetyl	82

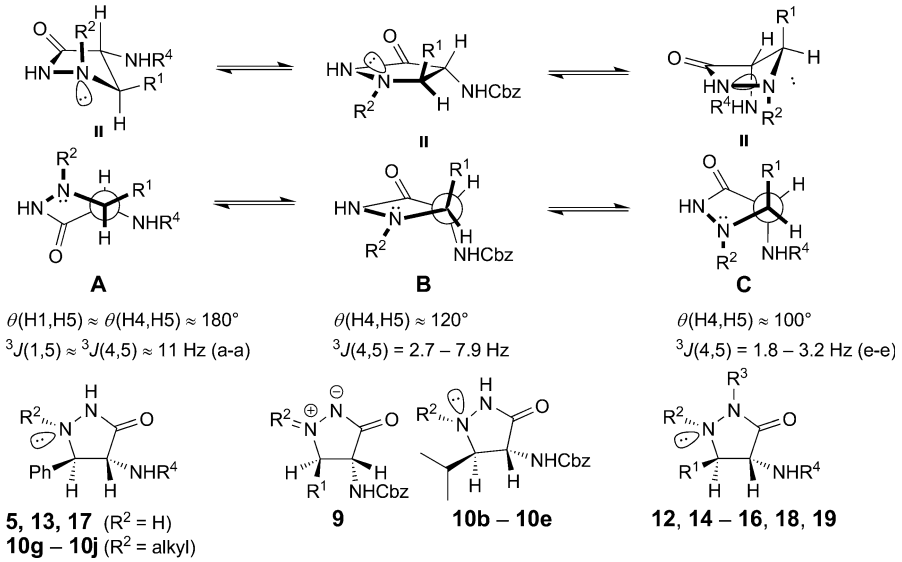


Fig. 2. *Conformations of 4-aminopyrazolidin-3-one derivatives* **5**, **9**, **10**, *and* **12**–**19** *in solution*

small number of required synthetic steps and building blocks (or reagents). In total, the title compounds are built up in two-to-five steps from phosphorylglycinate **4b**, $NH_2NH_2 \cdot H_2O$, aldehydes or ketones **6**, and alkyl halides **11**. The substitution pattern at N(1), C(5) and 4-NH_2 is controlled by the carbonyl compound **6**, and the substituent at N(2) by the alkyl halide **11**. In summary, this method enables an easy and diverse stepwise functionalization of 4-aminopyrazolidin-3-ones, therefore, it could also be

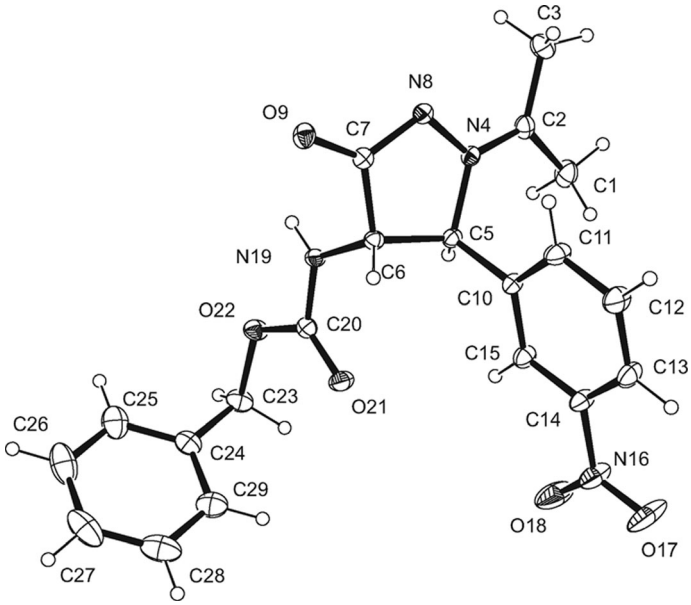


Fig. 3. *The molecular structure of* **9k**, *showing the atom labelling.* The displacement ellipsoids are drawn with 30% probability, and the H-atoms are shown as small spheres of arbitrary radii.

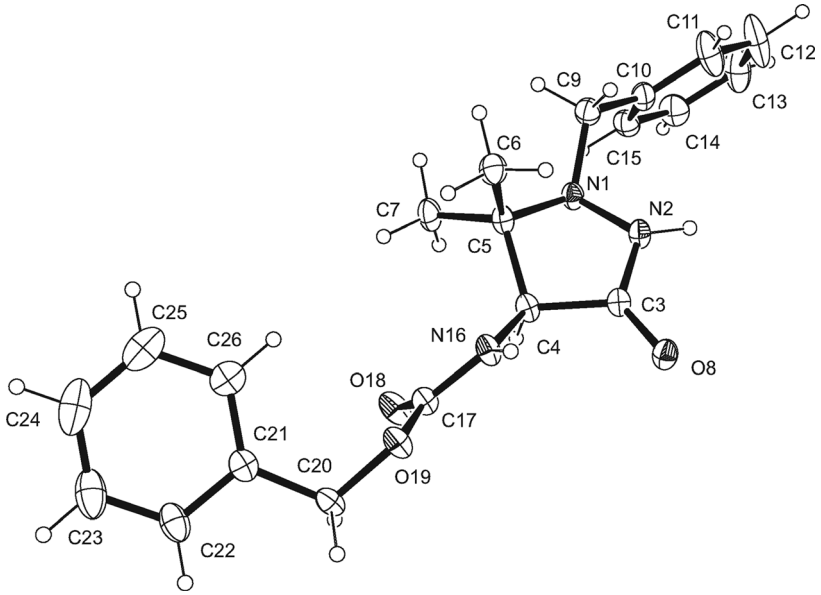


Fig. 4. *The molecular structure of* **10f**, *showing the atom labelling.* The displacement ellipsoids are drawn with 30% probability, and the H-atoms are indicated as small spheres of arbitrary radii.

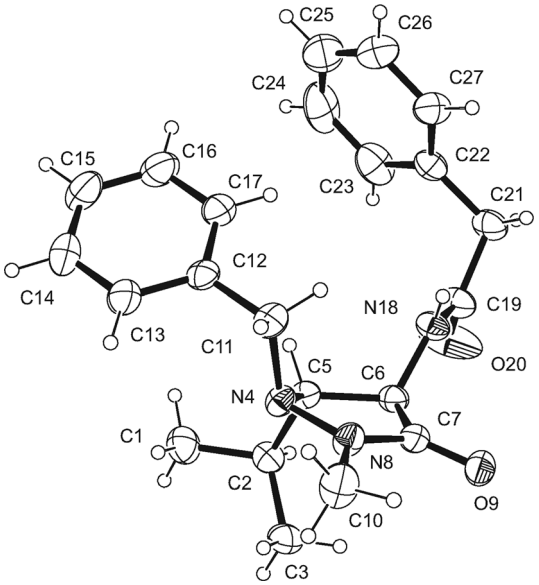


Fig. 5. *The molecular structure of* **18**, *showing the atom labelling*. The displacement ellipsoids are drawn with 30% probability, and the H-atoms are indicated as small spheres of arbitrary radii.

useful for the preparation of libraries of diversely functionalized pyrazolidin-3-ones in search for novel bioactive compounds and other applications.

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Experimental Part

1. *General.* Catalytic hydrogenations: *Parr Pressure Reaction Hydrogenation Apparatus 500 ml 3916EF*. Flash column chromatography (FC) and column chromatography (CC): silica gel (SiO_2; *Fluka*, silica gel *60*; particle size, 0.035–0.070 mm). TLC: Aluminium sheets, SiO_2 *60* F_{254} (*Fluka*). Medium-pressure liquid chromatography (MPLC): *Büchi Sepacore Flash Chromatography System* (*Büchi Fraction Collector C-660*, *Büchi Pump Module C-605*, *Büchi Control Unit C-620*) on SiO_2 (*Merck*, *LiChroprep® Si 60*; particle size, 0.015–0.025 mm); column dimensions, 36 × 460 mm; backpressure, 10 bar; detection, UV (254 nm). M.p.: *Kofler* micro hot stage and *Stanford Research Systems MPA100 OptiMelt* automated melting-point system; uncorrected. IR Spectra: *PerkinElmer Spectrum BX* FT-IR spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker Avance III UltraShield 500 plus* instrument (500 and 126 MHz, resp.) in (D_6)DMSO, $CDCl_3$, and (D_6)acetone; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS and HR-MS: *Agilent 6224 Accurate Mass TOF LC/MS* spectrometer; in *m*/*z*. Microanalyses: *PerkinElmer CHN Analyser 2400 II*.

2. *Starting Materials.* Aldehydes and ketones **6b**–**6r**, alkyl halides **11a**–**11d**, $NH_2NH_2 \cdot H_2O$, diazabicyclo[5.4.0]undec-7-ene (DBU), $NaBH_4$, $NaBH_3CN$, 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ), bis(pentafluorophenyl) carbonate (BPC), and 10% Pd/C are commercially available (*Sigma–Aldrich*). *Methyl* N-*[(benzyloxy)carbonyl]*-O-*tosyl*-L-*serinate* (**4a**) [27], *methyl 2-{[(benzyloxy)carbonyl]amino}-2-(dimethoxyphosphoryl)acetate* (**4b**) [28], 3-substituted methyl 2-{[(benzyloxy)carbonyl]amino}acrylates **7c**–**7f** [23], benzyl ((3*RS*,4*RS*)-3-substituted-5-oxopyrazolidin-

4-yl)carbamates **5c** [24] and **5f** [20], and (4*RS*,5*RS*)-1-[(*Z*)-arylmethylidene]-4-{[(benzyloxy)carbonyl]-amino}-3-oxo-5-substituted-pyrazolidin-1-ium-2-ides **9c**, **9d** [24] and **9h**, **9j** [20] were prepared according to the literature procedures.

3. *General Procedure for the Preparation of 3-Substituted Methyl 2-{[(Benzyloxy)carbonyl]amino}acrylates* **7** (*GP 1*). Compounds **7** were prepared according to a slightly modified literature procedure [23]. A mixture of **4b** (16.6 g, 50 mmol), CH_2Cl_2 (200 ml), DBU (52.5 mmol, 7.83 ml), and **6**[1]) (50 mmol) was stirred at r.t. for 3–24 h. Volatile components were evaporated *in vacuo*, and the residue was diluted with AcOEt (150 ml) and washed with 1M aq. $NaHSO_4$ (2 × 70 ml). The combined org. phase was dried (Na_2SO_4), filtered, and the filtrate was evaporated *in vacuo* to give **7**.

3.1. *Methyl (2*E*)-2-{[(Benzyloxy)carbonyl]amino}hex-2-enoate* (**7b**) [29]. Prepared from **4b** (6.6 g, 20 mmol) and **6b** (1.08 ml, 20 mmol), 3 h. Yield: 5.54 g (100%). Colorless oil. ([29a]: m.p. 38.5°). Spectroscopic data were in agreement with those in the literature [29b][29c].

3.2. *Methyl (2*Z*)-2-{[(Benzyloxy)carbonyl]amino}-3-(3-nitrophenyl)prop-2-enoate* (**7g**). Prepared from **4b** (1.65 g, 5 mmol) and **6g** (0.755 g, 5 mmol); 3 h. Yield: 0.73 g (41%). White solid. M.p. 105–109°. IR (KBr): 3545, 3468, 3412, 3287, 3234, 1715, 1697, 1617, 1531, 1455, 1409, 1352, 1293, 1239, 1214, 1147, 1061, 1029, 967, 899, 834, 818, 772, 738, 696, 618. ^{1}H-NMR ($CDCl_3$): 3.87 (*s*, Me); 5.07 (*s*, CH_2); 6.76 (br. *s*, NH); 7.23–7.40 (*m*, 5 H, Ph); 7.33 (*s*, H–C(3)); 7.46 (*t*, *J* = 8.0, 1 H, C_6H_4); 7.74 (*d*, *J* = 7.6, 1 H, C_6H_4); 8.12 (*d*, *J* = 8.1, 1 H, C_6H_4); 8.31 (*s*, 1 H, C_6H_4). ^{13}C-NMR ($CDCl_3$): 53.3; 68.1; 123.7; 124.2; 125.9; 127.2; 128.6; 128.7; 128.8; 129.5; 135.2; 135.7; 136.1; 148.4; 153.0; 165.3. ESI-MS: 357 ($[M+H]^+$). HR-ESI-MS: 357.1081 ($[M+H]^+$, $C_{18}H_{17}N_2O_6^+$; calc. 357.1081). Anal. calc. for $C_{18}H_{16}N_2O_6$ (356.33): C 60.67, H 4.53, N 7.86; found: C 60.87, H 4.61, N, 7.87.

3.3. *Methyl (2*Z*)-2-{[(Benzyloxy)carbonyl]amino}-3-(4-nitrophenyl)prop-2-enoate* (**7h**) [30]. Prepared from **4b** (3.31 g, 10 mmol) and **6h** (1.37 g, 9 mmol), 3 h. The crude **7h** was further purified by CC (AcOEt/hexanes 1:9). Yield: 2.1 g (58%). Yellow solid. M.p. 110–114° ([6]: m.p. 124–126°). IR (KBr): 3258, 1733, 1698, 1641, 1597, 1520, 1508, 1490, 1455, 1438, 1346, 1311, 1287, 1273, 1240, 1209, 1189, 1146, 1071, 863, 849, 770, 748, 695, 670. ^{1}H-NMR ($CDCl_3$): 3.87 (*s*, Me); 5.06 (*s*, CH_2); 6.78 (br. *s*, NH); 7.28–7.37 (*m*, 5 arom. H); 7.31 (*s*, H–C(3)); 7.55, 8.10 (2*d*, 1:1, *J* = 8.7, C_6H_4). ^{13}C-NMR ($CDCl_3$): 53.3; 68.0; 123.8; 126.6; 128.7; 128.7; 128.7; 128.8; 130.0; 130.0; 135.7; 141.0; 147.4; 165.2. ESI-MS: 357 ($[M+H]^+$). HR-ESI-MS: 357.1079 ($[M+H]^+$, $C_{18}H_{17}N_2O_6^+$; calc. 357.1081). Anal. calc. for $C_{18}H_{16}N_2O_6$ (356.33): C 60.67, H 4.53, N 7.86; found: C 60.42, H 4.43, N 7.83.

3.4. *Methyl (2*Z*)-2-{[(Benzyloxy)carbonyl]amino}-3-(4-chlorophenyl)prop-2-enoate* (**7i**) [31]. Prepared from **4b** (3.31 g, 10 mmol) and **6i** (1.69 g, 12 mmol); 3 h. Yield: 3.45 g (100%). Brown oil. IR (NaCl): 3260, 3068, 3033, 2952, 2980, 1718, 1691, 1645, 1591, 1508, 1488, 1455, 1437, 1404, 1389, 1375, 1313, 1266, 1212, 1144, 1088, 1064, 1029, 101, 993, 962, 918, 902, 875, 849, 824, 774, 752, 698, 652. ^{1}H-NMR ($CDCl_3$): 3.80 (*s*, Me); 5.09 (*s*, CH_2); 6.54 (br. *s*, NH); 7.25–7.42 (*m*, Ph, C_6H_4); 7.29 (*s*, H–C(3)). ^{13}C-NMR ($CDCl_3$): 53.0; 67.8; 124.4; 127.2; 128.5; 128.5; 128.7; 128.7; 129.0; 129.6; 131.1; 131.1; 165.8; 191.1. ESI-MS: 346 ($[M+H]^+$). HR-ESI-MS: 346.0845 ($[M+H]^+$, $C_{18}H_{17}ClNO_4^+$; calc. 346.0841).

3.5. *Methyl (2*Z*)-2-{[(Benzyloxy)carbonyl]amino}-3-(2-hydroxyphenyl)prop-2-enoate* (**7j**). Prepared from **4b** (6.29 g, 19 mmol) and **6j** (2 ml, 19 mmol), 3 h. Yield: 5.46 g (88%). Colorless oil. IR (NaCl): 3336, 3315, 3065, 3033, 2952, 2851, 1693, 1633, 1603, 1486, 1454, 1436, 1382, 1358, 1339, 1307, 1220, 113, 1102, 1048, 1027, 992, 945, 898, 852, 816, 752, 696, 617. ^{1}H-NMR ($CDCl_3$): 3.74 (*s*, Me); 5.10 (*s*, CH_2); 5.23 (*s*, OH); 6.80–6.90 (*m*, 2 arom. H); 7.27–7.43 (*m*, 7 arom. H); 7.32 (*s*, H–C(3)). ^{13}C-NMR ($CDCl_3$): 52.8; 67.9; 116.8; 120.6; 128.4; 128.5; 128.7; 128.9; 130.8; 133.9; 137.2; 153.8; 158.7; 166.0. ESI-MS: 328 ($[M+H]^+$). HR-ESI-MS: 328.1185 ($[M+H]^+$, $C_{18}H_{18}NO_5^+$; calc. 328.1179).

3.6. *Methyl (2*Z*)-2-{[(Benzyloxy)carbonyl]amino}-3-(3,4,5-trimethoxyphenyl)prop-2-enoate* (**7k**). Prepared from **4b** (3.31 g, 10 mmol) and **6k** (1.78 g, 9.1 mmol), 3 h. The crude **7k** was purified by CC (AcOEt/hexanes 1:9). Yield: 2.22 g (55%). White solid. M.p. 114–119°. IR (KBr): 3305, 2997, 2946, 2842, 1719, 1639, 1581, 1505, 1455, 1435, 1418, 1388, 1334, 1312, 1262, 1240, 1191, 1159, 1128, 1053, 1001,

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[1]) In the reactions of **4b** with acetone **6d** and cyclohexanone **6e**, these two ketones were also used as solvents (200 ml each) instead of CH_2Cl_2.

755, 698, 667. ^{1}H-NMR ($CDCl_3$): 3.72, 3.83, 3.87 (4*s*, 1:2:1, 4 Me); 5.13 (*s*, CH_2); 6.30 (br. *s*, NH); 6.78 (*s*, C_6H_2); 7.31 (*s*, H–C(3)); 7.32–7.40 (*m*, Ph). ^{13}C-NMR ($CDCl_3$): 52.8; 56.0; 56.0; 61.0; 67.7; 107.2; 107.2; 123.5; 128.3; 128.5; 128.7; 129.0; 132.6; 136.0; 139.3; 153.1; 153.1; 154.1; 165.9. ESI-MS: 402 ($[M+H]^+$). HR-ESI-MS: 402.1541 ($[M+H]^+$, $C_{21}H_{24}NO_7^+$; calc. 402.1547).

4. *Benzyl (4*RS*)-(3-Oxopyrazolidin-4-yl)carbamate* (**5a**). This compound was prepared following a slightly modified literature procedure for the synthesis of the *t*-Bu analog [22]. A mixture of **4a** (4.07 g, 10 mmol), MeOH (50 ml), and $NH_2NH_2 \cdot H_2O$ (1.5 ml, 30 mmol) was refluxed for 1 h. The volatile components were evaporated *in vacuo*, the residue was taken up in 1M aq. $NaHCO_3$ (30 ml), and the product was isolated by continuous extraction with $CHCl_3$ (100 ml). The precipitate was collected by filtration to give **5** [1]. Yield: 1.46 g (62%). Beige solid. M.p. 151–154° ([21]: 155–156°).

5. *General Procedures for the Preparation of Pyrazolidin-3-ones* **5** (*GP 2*). A mixture of **7** (20 mmol), alcohol (30 ml), and $NH_2NH_2 \cdot H_2O$ (3–5 equiv.) was stirred at r.t. or at reflux for 3–336 h.

Workup A: General Procedure 2A (*GP 2A*). The precipitate was collected by filtration and washed with the mother liquor and hexanes to give **5**.

Workup B: General Procedure 2B (*GP 2B*). Volatile components were evaporated *in vacuo*, and the residue was purified by CC (AcOEt). Fractions containing the product were combined and evaporated *in vacuo* to give **5**.

5.1. *Benzyl [(4*RS*,5*RS*)-3-Oxo-5-propylpyrazolidin-4-yl]carbamate* (**5b**). Prepared from **7b** (4.33 g, 15.6 mmol), $NH_2NH_2 \cdot H_2O$ (2.28 ml, 47 mmol), and PrOH (30 ml); r.t. for 3 h; *GP 2A*. Yield: 1.94 g (45%). White solid. M.p. 178–182°. IR (KBr): 3440, 3327, 3207, 2959, 2932, 1718, 1695, 1661, 1639, 1541, 1456, 1420, 1364, 1297, 1279, 1257, 1241, 1168, 1064, 776, 755, 730, 696. ^{1}H-NMR ((D_6)DMSO): 0.85 (*t*, *J* = 7.3, Me); 1.20–1.41, 1.42–1.58 (2*m*, 1:1, 2 CH_2); 3.15 (*dt*, *J* = 6.7, 11.1, H–C(5)); 3.95 (*dd*, *J* = 9.5, 11.1, H–C(4)); 4.90 (*d*, *J* = 11.4, H–N(1)); 5.04, 5.06 (2*d*, 1:1, *J* = 12.4, CH_2); 7.28–7.40 (*m*, 5 arom. H); 7.54 (*d*, *J* = 9.5, HN–C(4)); 9.21 (*s*, H–N(2)). ^{13}C-NMR ((D_6)DMSO): 14.0; 18.8; 32.9; 57.7; 62.8; 65.5; 127.7; 127.9; 128.4; 137.1; 156.3; 173.9. ESI-MS: 278 ($[M+H]^+$). HR-ESI-MS: 278.1501 ($[M+H]^+$, $C_{14}H_{20}N_3O_3^+$; calc. 278.1505). Anal. calc. for $C_{14}H_{19}N_3O_3 \cdot 1/5\ H_2O$ (280.92): C 59.86, H 6.96, N 14.96; found: C 59.83, H 6.61, N 15.07.

5.2. *Benzyl [(4*RS*)-3,3-Dimethyl-5-oxopyrazolidin-4-yl]carbamate* (**5d**). Prepared from **7d** (5.26 g, 20 mmol), $NH_2NH_2 \cdot H_2O$ (2.92 ml, 60 mmol), and PrOH (30 ml); reflux for 10 h; *GP 2B*. Yield: 3.66 g (69%). White solid. M.p. 122–129°. IR (KBr): 3293, 3216, 3067, 3036, 2974, 2937, 1728, 1688, 1680, 1545, 1497, 1448, 1388, 1369, 1326, 1262, 1249, 1217, 1052, 1020, 1009, 982, 881, 805, 774, 756, 699. ^{1}H-NMR ((D_6)DMSO): 0.91, 1.15 (2*s*, 1:1, 2 Me); 4.16 (*d*, *J* = 9.4, H–C(4)); 5.06 (*s*, CH_2); 5.07 (*d*, *J* = 3.8, H–N(1)); 7.29–7.41 (*m*, 5 arom. H); 7.47 (*d*, *J* = 9.4, HN–C(4)); 9.14 (*s*, H–N(2)). ^{13}C-NMR ((D_6)DMSO): 20.3; 23.9; 30.7; 61.1; 65.7; 127.8; 127.9; 128.4; 137.0; 156.8; 174.2. ESI-MS: 264 ($[M+H]^+$). HR-ESI-MS: 264.1339 ($[M+H]^+$, $C_{13}H_{18}N_3O_3^+$; calc. 264.1348). Anal. calc. for $C_{13}H_{17}N_3O_3$ (263.29): C 59.30, H 6.51, N 15.96; found: C 59.50, H 6.31, N 15.74.

5.3. *Benzyl [(4*RS*)-3-Oxo-1,2-diazaspiro[4.5]dec-4-yl]carbamate* (**5e**). Prepared from **7e** (303 mg, 1 mmol), $NH_2NH_2 \cdot H_2O$ (0.146 ml, 3 mmol), and EtOH (1.5 ml), r.t. for 336 h, *GP 2B*. Yield: 70 mg (23%). White solid. M.p. 160–164°. IR (KBr): 3297, 3230, 3066, 3066, 2936, 2850, 1728, 1682, 1544, 1448, 1386, 1264, 1243, 1217, 1098, 1080, 1050, 754, 698. ^{1}H-NMR ($CDCl_3$): 1.09–1.33 (*m*, CH_2); 1.38–1.69 (*m*, 3 CH_2); 1.75 (*d*, *J* = 14.2, 1 H, CH_2); 1.96 (*dt*, *J* = 3.7, 13.9, 1 H, CH_2); 3.91 (*s*, H–N(1)); 4.29 (*d*, *J* = 6.9, H–C(4)); 5.11, 5.15 (2*d*, 1:1, *J* = 12.2, CH_2); 5.21 (*d*, *J* = 6.9, HN–C(4)); 6.91 (*s*, H–N(2)); 7.27–7.47 (*m*, 5 arom. H). ^{13}C-NMR ((D_6)DMSO): 21.3; 22.0; 25.6; 26.8; 35.1; 61.7; 66.6; 67.6; 128.4; 128.5; 128.8; 136.2; 157.0; 175.8. ESI-MS: 304 ($[M+H]^+$). HR-ESI-MS: 304.1655 ($[M+H]^+$, $C_{16}H_{22}N_3O_3^+$; calc. 304.1656). Anal. calc. for $C_{16}H_{21}N_3O_3$ (303.36): C 63.35, H 6.98, N 13.85; found: C 63.12, H 7.09, N 13.78.

5.4. *Benzyl [(3*RS*,4*RS*)-3-(3-Nitrophenyl)-5-oxopyrazolidin-4-yl]carbamate* (**5g**). Prepared from **7g** (1.78 g, 5 mmol), $NH_2NH_2 \cdot H_2O$ (2.28 ml, 47 mmol), and EtOH (13 ml); r.t. for 5 h; *GP 2A*. Yield: 780 mg (44%). Yellow solid. M.p. 146–151°. IR (KBr): 3260, 1726, 1695, 1646, 1616, 1574, 1527, 1506, 1480, 1458, 1440, 1354, 1310, 1285, 1256, 1240, 1214, 1144, 1088, 1064, 998, 929, 865, 826, 773, 752, 735, 701, 670. ^{1}H-NMR ((D_6)DMSO): 4.42 (*t*, *J* = 9.7, H–C(4)); 4.50 (*t*, *J* = 10.4, H–C(5)); 5.03 (br. *s*, CH_2); 5.66 (*d*, *J* = 10.4, H–N(1)); 7.26–7.38 (*m*, 5 arom. H); 7.70 (br. *t*, *J* = 7.9, 1 H, C_6H_4); 7.81 (br. *d*, *J* = 8.6, HN–C(4)); 7.70 (br. *d*, *J* = 7.8, 1 H, C_6H_4); 8.18–8.24 (*m*, 1 H, C_6H_4); 8.34 (br. *t*, *J* = 2.0, 1 H, C_6H_4); 9.62 (*s*, H–N(2)). ^{13}C-NMR ((D_6)DMSO): 58.0; 65.0; 65.7; 121.9; 123.1; 127.7; 127.9; 128.4; 130.2; 134.1; 136.8;

139.4; 147.9; 156.2; 172.1. ESI-MS: 357 ($[M+H]^+$). HR-ESI-MS: 357.12 ($[M+H]^+$, $C_{17}H_{17}N_4O_5^+$; calc. 357.1193). Anal. calc. for $C_{17}H_{16}N_4O_5$ (356.33): C 57.30, H 4.53, N 15.72; found: C 57.06, H 4.43, N 15.64.

5.5. *Benzyl [(3*RS*,4*RS*)-3-(4-Nitrophenyl)-5-oxopyrazolidin-4-yl]carbamate* (**5h**). Prepared from **7h** (356 mg, 1 mmol), $NH_2NH_2 \cdot H_2O$ (0.146 ml, 3 mmol), and EtOH (5 ml); r.t. for 24 h; *GP 2A*. Yield: 356 mg (100%). Yellow solid. M.p. 184–190°. IR (KBr): 3478, 3411, 3340, 3234, 3183, 1719, 1697, 1606, 1521, 1456, 1348, 1288, 1242, 1181, 1148, 1108, 1052, 952, 850, 832, 748, 698, 669. ^{1}H-NMR ((D$_6$)DMSO): 4.39 (*t*, *J* = 9.9, H–C(4)); 4.48 (*t*, *J* = 10.7, H–C(5)); 5.01, 5.04 (2*d*, 1:1, *J* = 12.6, CH_2); 5.67 (*d*, *J* = 10.7, H–N(1)); 7.25–7.40 (*m*, 5 arom. H); 7.72 (*d*, *J* = 8.5, 2 H, C_6H_4); 7.83 (*d*, *J* = 9.9, HN–C(4)); 8.25 (*d*, *J* = 8.5, 2 H, C_6H_4); 9.7 (br. *s*, H–N(2)). ^{13}C-NMR ((D$_6$)DMSO): 58.1; 65.2; 65.8; 123.7; 127.8; 128.0; 128.4; 128.6; 136.8; 144.9; 147.3; 156.2; 172.0. ESI-MS: 357 ($[M+H]^+$). HR-ESI-MS: 357.1195 ($[M+H]^+$, $C_{17}H_{17}N_4O_5^+$; calc. 357.1193). Anal. calc. for $C_{17}H_{16}N_4O_5 \cdot 1/5\ H_2O$ (359.54): C 56.73, H 4.59, N 15.57; found: C 56.56, H 4.22, N 15.51.

5.6. *Benzyl [(3*RS*,4*RS*)-3-(4-Chlorophenyl)-5-oxopyrazolidin-4-yl]carbamate* (**5i**). Prepared from **7i** (417 mg, 1.2 mmol), $NH_2NH_2 \cdot H_2O$ (0.176 ml, 3.6 mmol), and MeOH (2 ml); r.t. for 24 h; *GP 2A*. Yield: 148 mg (43%). Pale-yellow solid. M.p. 193–197°. IR (KBr): 3336, 3217, 3188, 1780, 1719, 1694, 1660, 1538, 1494, 1466, 1454, 1418, 1356, 1292, 1244, 1216, 1201, 1181, 1152, 1091, 1071, 1056, 1028, 1015, 963, 917, 857, 827, 773, 732, 707, 694, 645. ^{1}H-NMR ((D$_6$)DMSO): 4.32 (*t*, *J* = 11.1, H–C(5)); 4.40 (*dd*, *J* = 9.0, 11.1, H–C(4)); 4.99, 5.05 (2*d*, 1:1, *J* = 12.5, CH_2); 5.44 (*d*, *J* = 11.1, H–N(1)); 7.30–7.37 (*m*, 5 H, Ph); 7.43–7.48 (*m*, 4 H, C_6H_4); 7.73 (*d*, *J* = 9.0, HN–C(4)); 9.54 (*s*, H–N(2)). ^{13}C-NMR ((D$_6$)DMSO): 57.7; 65.3; 65.6; 127.8; 128.3; 128.5; 129.3; 131.1; 132.7; 135.9; 136.8; 156.2; 172.6. ESI-MS: 346 ($[M+H]^+$). HR-ESI-MS: 346.0951 ($[M+H]^+$, $C_{17}H_{17}ClN_3O_3^+$; calc. 346.0953).

5.7. *Benzyl [(3*RS*,4*RS*)-3-(2-Hydroxyphenyl)-5-oxopyrazolidin-4-yl]carbamate* (**5j**). Prepared from **7j** (4.08 g, 12.5 mmol), $NH_2NH_2 \cdot H_2O$ (2.44 ml, 50 mmol), and EtOH (40 ml); r.t. for 24 h; *GP 2A*[2]). Yield: 1.99 g (49%). White solid. M.p. 110–115°. IR (KBr): 3324, 2929, 1728, 1696, 1632, 1606, 1573, 1536, 1489, 1459, 1450, 1382, 1360, 1321, 1297, 1277, 1248, 1229, 1205, 1183, 1166, 1119, 1085, 1042, 1000, 992, 943, 926, 891, 852, 758, 738, 715, 696. ^{1}H-NMR ((D$_6$)DMSO): 4.51 (*t*, *J* = 10.9, H–C(5)); 4.65 (br. *t*, *J* = 10.0, H–C(4)); 4.95, 5.00 (2*d*, 1:1, *J* = 12.5, CH_2); 5.23 (br. *d*, *J* = 11.3, H–N(1)); 6.79 (*t*, *J* = 7.5, 1 H, C_6H_4); 6.84 (*t*, *J* = 8.0, 1 H, C_6H_4); 6.84 (*t*, *J* = 8.0, 1 H, C_6H_4); 7.15 (*dt*, *J* = 1.7, 7.7, 1 H, C_6H_4); 7.27–7.38 (*m*, 5 arom. H); 7.62 (*d*, *J* = 9.2, HN–C(4)); 9.44 (*s*, H–N(2)); 9.88 (*s*, OH). ^{13}C-NMR ((D$_6$)DMSO): 55.6, 64.1, 65.4, 115.6, 118.4, 119.0, 123.8, 127.8, 128.3, 128.3, 136.9, 137.0, 156.1, 156.3, 169.2. ESI-MS: 328 ($[M+H]^+$). HR-ESI-MS: 328.1285 ($[M+H]^+$, $C_{17}H_{18}N_3O_4^+$; calc. 328.1292).

6. *General Procedures for the Preparation of Azomethine Imines* **9** (*GP 3*). Compounds **9** were prepared following a slightly modified literature procedure [20][24]. A mixture of **5** (1 mmol), MeOH (4 ml), and **6** (1.2 mmol) was stirred at r.t. for 5 min. Then, CF_3COOH (TFA, 2 drops) was added, and the mixture was stirred at r.t. or at reflux for 1–24 h.

Workup A: General Procedure 3A (*GP 3A*). The precipitate was collected by filtration and washed with EtOH (2 ml) and Et_2O (5 ml) to give **9**.

Workup B: General Procedure 3B (*GP 3B*). Volatile components were evaporated *in vacuo*, and the residue was purified by CC (AcOEt/EtOH). Fractions containing the product were combined, and the solvent was evaporated *in vacuo* to give **9**.

6.1. *(2Z,4*RS*)-2-Benzylidene-4-{[(benzyloxy)carbonyl]amino}-5-oxopyrazolidin-2-ium-1-ide* (**9a**). Prepared from **5a** (0.118 g, 0.5 mmol), **6f** (0.061 ml, 0.5 mmol), and MeOH (5 ml); r.t. for 24 h; *GP 3A*. Yield: 50 mg (31%). Pale-yellow solid. M.p. 175–177°. IR (KBr): 3419, 3216, 3028, 2959, 1703, 1664, 1600, 1539, 1494, 1452, 1430, 1370, 1325, 1305, 1264, 1212, 1153, 1114, 1085, 1011, 1000, 936, 871, 851, 768, 729, 701, 658, 614. ^{1}H-NMR ((D$_6$)DMSO): 4.31 (*dd*, *J* = 6.5, 13.4, H_a–C(5)); 4.41–4.47 (*m*, H–C(4)); 4.83 (*dd*, *J* = 9.6, 13.4, H_b–C(5)); 5.05 (*s*, CH_2); 7.29–7.41 (*m*, 5 arom. H); 7.50–7.59 (*m*, 3 arom. H); 7.73 (*s*, H–C(1′)); 7.82 (*d*, *J* = 8.0, HN–C(4)); 8.26–8.35 (*m*, 2 arom. H); ^{13}C-NMR ((D$_6$)DMSO): 50.2; 61.5; 65.6; 127.8; 127.9; 128.4; 128.8; 129.6; 131.2; 131.5; 133.3; 136.9; 156.0; 181.6. ESI-MS: 324

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[2]) H_2O (50 ml) was added to induce precipitation.

([$M+H$]$^+$). HR-ESI-MS: 324.1346 ([$M+H$]$^+$, $C_{18}H_{18}N_3O_3^+$; calc. 324.1343). Anal. calc. for $C_{18}H_{17}N_3O_3$ (323.35): C 66.86, H 5.30, N 13.00; found: C 66.61, H 5.42, N 13.13.

6.2. *(2Z,3*RS*,4*RS*)-2-Benzylidene-4-{[(benzyloxy)carbonyl]amino}-5-oxo-3-propylpyrazolidin-2-ium-1-ide* (**9b**). Prepared from **5b** (0.277 g, 1 mmol), **6f** (0.122 ml, 1.2 mmol), and MeOH (5 ml); reflux for 12 h; *GP 3A*. Yield: 210 mg (58%). Yellow solid. M.p. 177–181°. IR (KBr): 3184, 3055, 2960, 2874, 1718, 1656, 1591, 1569, 1557, 1456, 1438, 1362, 1326, 1268, 1156, 1096, 1036, 1006, 758, 737, 689. ^{1}H-NMR ((D$_6$)DMSO): 0.93 (*t*, *J* = 7.1, Me); 1.37–1.47 (*m*, 2 H, Pr); 1.84–1.95, 2.05–2.18 (2*m*, 1:1, 2 H, Pr); 4.12 (*dd*, *J* = 4.1, 8.4, H–C(4)); 4.49 (*dt*, *J* = 4.1, 8.5, H–C(5)); 5.05 (*s*, CH$_2$); 7.19–7.40 (*m*, 5 arom. H); 7.54–7.56 (*m*, 3 arom. H); 7.79 (*s*, H–C(1′)); 7.89 (*d*, *J* = 8.4, HN–C(4)); 8.34–8.36 (*m*, 2 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 13.6; 17.4; 35.4; 55.5; 65.6; 73.4; 127.8; 127.9; 128.4; 128.7; 129.7; 131.5; 131.6; 133.2; 136.9; 155.9; 180.1. ESI-MS: 366 ([$M+H$]$^+$). HR-ESI-MS: 366.1804 ([$M+H$]$^+$, $C_{21}H_{24}N_3O_3^+$; calc. 366.1818). Anal. calc. for $C_{21}H_{23}N_3O_3 \cdot 1/6\ H_2O$ (368.43): C 68.46, H 6.38, N 11.41; found: C 69.02, H 6.34, N 11.50.

6.3. *(2Z,4*RS*)-2-Benzylidene-4-{[(benzyloxy)carbonyl]amino}-3,3-dimethyl-5-oxopyrazolidin-2-ium-1-ide* (**9e**). Prepared from **5d** (1.32 g, 5 mmol), **6f** (0.61 ml, 6 mmol), and MeOH (25 ml); reflux fot 3 h; *GP 3A*. Yield: 1.35 g (77%). Pale-yellow solid. M.p. 200–204°. IR (KBr): 3549, 3466, 3412, 3311, 3048, 2975, 2958, 1720, 1699, 1666, 1593, 1570, 1541, 1453, 1418, 1399, 1377, 1360, 1327, 1304, 1277, 1239, 1214, 1083, 1069, 1050, 984, 908, 758,3 694, 676, 648. ^{1}H-NMR ((D$_6$)DMSO): 1.42, 1.75 (2*s*, 1:1, 2 Me); 4.37 (*d*, *J* = 8.9, H–C(4)); 5.07, 5.12 (2*d*, 1:1, *J* = 12.6, CH$_2$); 7.31–7.39 (*m*, 5 arom. H); 7.54 (*m*, 3 arom. H); 7.83 (*d*, *J* = 8.8, HN–C(4)); 7.87 (*s*, H–C(1′)); 8.39 (*dd*, *J* = 2.9, 6.8, 2 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 23.5; 27.0; 59.8; 65.8; 75.0; 127.8; 127.9; 128.4; 128.7; 129.9; 131.6; 131.7; 132.0; 136.9; 156.9; 178.5. ESI-MS: 352 ([$M+H$]$^+$). HR-ESI-MS: 352.1659 ([$M+H$]$^+$, $C_{20}H_{22}N_3O_3^+$; calc. 352.1661). Anal. calc. for $C_{20}H_{21}N_3O_3$ (351.40): C 68.36, H 6.02, N 11.96; found: C 68.08, H 5.77, N 11.75.

6.4. *(2Z,4*RS*)-4-{[(Benzyloxy)carbonyl]amino}-2-(2,6-dichlorobenzylidene)-3,3-dimethyl-5-oxopyrazolidin-2-ium-1-ide* (**9f**). Prepared from **5d** (527 mg, 2 mmol), **6l** (0.42 g, 2.4 mmol), and MeOH (40 ml); reflux for 4.5 h; *GP 3A*. Yield: 508 mg (60%). Pale-yellow solid. M.p. 195–199°. IR (KBr): 3284, 3038, 2979, 2935, 1730, 1702, 1679, 1587, 1538, 1498, 1455, 1432, 1397, 1373, 1348, 1311, 1279, 1234, 1392, 1108, 1082, 1058, 1013, 930, 879, 816, 774, 734, 965. ^{1}H-NMR (CDCl$_3$): 1.60, 2.05 (2*s*, 1:1, 2 Me); 4.52 (*d*, *J* = 4.3, H–C(4)); 5.12, 5.16 (2*d*, 1:1, *J* = 12.3, CH$_2$); 5.53 (*d*, *J* = 3.4, NH); 7.30–7.40 (*m*, 8 H, Ph, C$_6$H$_3$); 7.35 (*s*, H–C(1′)). ^{13}C-NMR (CDCl$_3$): 24.6; 27.0; 61.3; 67.5; 77.8; 127.8; 128.1; 128.2; 128.2; 128.3; 128.4; 128.4; 128.8; 132.2; 134.8; 136.1; 157.5; 179.0. ESI-MS: 420 ([$M+H$]$^+$). HR-ESI-MS: 420.0879 ([$M+H$]$^+$, $C_{20}H_{20}Cl_2N_3O_3^+$; calc. 420.0876). Anal. calc. for $C_{20}H_{19}Cl_2N_3O_3$ (420.29): C 57.15, H 4.56, N 10.00; found: C 56.88, H 4.40, N 9.96.

6.5. *(3*RS*,4*RS*)-4-{[(Benzyloxy)carbonyl]amino}-5-oxo-3-phenyl-2-(propan-2-ylidene)pyrazolidin-2-ium-1-ide* (**9g**). Prepared from **5f** (0.31 g, 1 mmol), **6d** (1 ml), and MeOH (4 ml); r.t. for 24 h; *GP 3B*, AcOEt/EtOH 5:1. Yield: 0.30 g (86%). White solid. M.p. 176–177°. IR (KBr): 3458, 3202, 3030, 2978, 2923, 1724, 1674, 1607, 1566, 1498, 1489, 1454, 1438, 1372, 1357, 1298, 1267, 1152, 1124, 1094, 1063, 1024, 778, 764, 732, 708, 694, 654. ^{1}H-NMR ((D$_6$)DMSO): 1.96, 2.31 (2*s*, 1:1, Me); 3.90 (*dd*, *J* = 2.7, 8.0, H–C(4)); 5.04, 5.08 (2*d*, 1:1, *J* = 12.5, CH$_2$); 5.70 (br. *s*, H–C(5)); 7.24–7.47 (*m*, 10 arom. H); 8.11 (*d*, *J* = 8.0, NH). ^{13}C-NMR ((D$_6$)DMSO): 20.8; 22.3; 62.7; 65.7; 73.5; 125.3; 127.9; 127.9; 128.4; 128.4; 129.4; 136.8; 137.7; 151.9; 156.1; 176.7. ESI-MS: 352 ([$M+H$]$^+$). HR-ESI-MS: 352.1644 ([$M+H$]$^+$, $C_{20}H_{22}N_3O_3^+$; calc. 352.1661). Anal. calc. for $C_{20}H_{21}N_3O_3 \cdot 1/4\ H_2O$ (355.90): C 67.49, H 6.09, N 11.81; found: C 67.49, H 6.07, N 11.72.

6.6. *(2Z,3*RS*,4*RS*)-4-{[(Benzyloxy)carbonyl]amino}-5-oxo-3-phenyl-2-(3,4,5-trimethoxybenzylidene)pyrazolidin-2-ium-1-ide* (**9i**). Prepared from **5f** (0.31 g, 1 mmol), **6k** (236 mg, 1.2 mmol), and EtOH (4 ml); reflux for 1 h; *GP 3A*. Yield: 385 mg (79%). Pale-yellow solid. M.p. 159–163°. IR (KBr): 3411, 3027, 3007, 2970, 2940, 1715, 1662, 1595, 1504, 1456, 1427, 1375, 1334, 1272, 1249, 1159, 1128, 1041, 1002, 778, 743, 697, 643. ^{1}H-NMR (CDCl$_3$): 3.86, 3.91 (2*s*, 2:1, 3 Me); 4.53 (br. *t*, *J* = 5.4, H–C(4)); 5.08 (*s*, CH$_2$); 5.55 (br. *d*, *J* = 5.4, H–C(5)); 6.06 (br. *s*, NH); 6.75 (*s*, H–C(1′)); 7.20–7.54 (*m*, 12 H, Ph, C$_6$H$_2$). ^{13}C-NMR (CDCl$_3$): 56.6; 60.6; 61.3; 67.4; 79.6; 106.9; 109.8; 124.0; 127.6; 128.2; 128.4; 128.7; 129.9; 136.2; 136.5; 142.3; 153.2; 153.8; 179.3; 191.3. ESI-MS: 490 ([$M+H$]$^+$). HR-ESI-MS: 490.1969 ([$M+H$]$^+$, $C_{27}H_{28}N_3O_6^+$; calc. 490.1973). Anal. calc. for $C_{27}H_{27}N_3O_6 \cdot 1/3\ H_2O$ (459.52): C 65.44 H, 5.63, N 8.48; found: C 65.27, H 5.87, N 8.50.

6.7. *(3*RS*,4*RS*)-4-{[(Benzyloxy)carbonyl]amino}-3-(3-nitrophenyl)-5-oxo-2-[(*$^2H_6$*)propan-2-ylidene]pyrazolidin-2-ium-1-ide* (**9k**). A mixture of **5g** (178 mg, 0.5 mmol) and (D_6)acetone **6m** (1 ml) was stirred at r.t. for 24 h. The precipitate was collected by filtration to give **9k**. Yield: 151 mg (75%). White solid. M.p. 200–204°. ^{1}H- and ^{13}C-NMR spectra could not be recorded due to insolubility of the product in various solvents including (D_6)DMSO. IR (KBr): 3087, 3032, 3002, 2969, 1697, 1669, 1615, 1527, 1456, 1419, 1351, 1307, 1260, 1219, 1166, 1110, 1084, 1068, 1038, 978, 958, 923, 895, 828, 810, 781, 758, 739, 716, 701, 685, 670. ESI-MS: 403 ($[M+H]^+$). HR-ESI-MS: 403.1875 ($[M+H]^+$, $C_{20}H_{14}D_6N_4O_5^+$; calc. 403.188).

7. *Synthesis of Benzyl [(4*RS*,5*RS*)-1-Benzyl-3-oxo-5-(propan-2-yl)pyrazolidin-4-yl]carbamate* (**10e**). A stirred suspension of **9c** (0.744 g, 2 mmol) in MeOH (8 ml) was stirred at 0° for 10 min. Then, $NaBH_4$ (0.115 g, 3 mmol) was added slowly (portionwise), and the mixture was stirred at 0° for 2 h and at r.t. for 2 h. H_2O (30 ml) was added, and the product was extracted with CH_2Cl_2 (5 × 20 ml). The combined org. phases were dried (Na_2SO_4), filtered, and the filtrate was evaporated *in vacuo* to give **10e**. Yield: 0.692 g (93%). White solid. M.p. 138–142°. IR (KBr): 3267, 3065, 3035, 2959, 2872, 1725, 1693, 1687, 1558, 1550, 1542, 1497, 1455, 1275, 1261, 1172, 1027, 732, 698, 669. ^{1}H-NMR ((D_6)DMSO): 0.78, 0.83 (2*d*, 1:1, *J* = 6.8, 3 H, ^{i}Pr); 1.66 (*sept.*, *J* = 6.5, 1 H, ^{i}Pr); 2.78 (*t*, *J* = 6.0, H–C(5)); 3.84, 3.92 (2*d*, 1:1, *J* = 12.9, CH_2); 3.95 (*dd*, *J* = 6.6, 8.8, H–C(4)); 5.02 (*s*, CH_2); 7.26–7.38 (*m*, 10 arom. H); 7.96 (*d*, *J* = 8.7, NH); 9.63 (*s*, H–N(2)). ^{13}C-NMR ((D_6)DMSO): 17.3; 18.3; 29.9; 53.6; 63.4; 65.6; 72.1; 127.4; 127.8; 127.9; 128.2; 128.4; 129.4; 136.8; 137.0; 155.8; 169.0. ESI-MS: 368 ($[M+H]^+$). HR-ESI-MS: 368.1964 ($[M+H]^+$, $C_{21}H_{26}N_3O_3^+$; calc. 368.1974). Anal. calc. for $C_{21}H_{25}N_3O_3$ (367.44): C 68.64, H 6.86, N 11.44; found: C 68.39, H 6.49, N 11.46.

8. *General One-Pot Procedure for the Synthesis of 1,5-Disubstituted (4*RS*,5*RS*)-4-{[(Benzyloxy)carbonyl]amino}pyrazolidin-3-ones* **10** (*GP 4*). A mixture of **5** (1 mmol), MeOH (5 ml), **6** (1.2 mmol), and CF_3COOH (2 drops) was stirred at r.t. for 10 min. Then, $NaBH_4$ (0.046 g, 1.2 mmol) or $NaBH_3CN$ (0.076 g, 1.2 mmol) was added, and the mixture was stirred at r.t. or under reflux for 3–100 h.

Workup A: General Procedure 4A (*GP 4A*). The precipitate was collected by filtration and washed with Et_2O (5 ml) to give **10**.

Workup B: General Procedure 4B (*GP 4B*). Volatile components were evaporated *in vacuo*, and the residue was purified by CC (AcOEt/hexanes). Fractions containing the product were combined and evaporated *in vacuo* to give **10**.

8.1. *Benzyl [(4*RS*)-3-Oxo-1-(propan-2-yl)pyrazolidin-4-yl]carbamate* (**10a**). Prepared from **5a** (3.81 g, 16 mmol), **6d** (20 ml), and $NaBH_4$ (850 mg, 22.5 mmol); r.t. for 48 h; *GP 4A*. Yield: 5.81 mg (90%). Pale-yellow solid. M.p. 132–135°. IR (KBr): 3554, 3418, 3308, 3064, 2980, 2811, 1682, 1617, 1548, 1530, 1454, 1390, 1368, 1340, 1291, 1279, 1242, 1176, 1081, 1064, 1026, 1009, 902, 875, 845, 783, 755, 739, 697. ^{1}H-NMR ((D_6)DMSO): 0.97, 1.00 (2*d*, 1:1, *J* = 6.3, *Me*$_2$CH); 2.74, 2.85 (2 br. *s*, 1:1, CH_2); 3.50 (*dd*, *J* = 10.9, 8.6, H–C(4)); 4.31–4.42 (br. *m*, Me_2CH); 5.04 (*s*, CH_2); 7.27–7.41 (*m*, 5 arom. H); 7.61 (*d*, *J* = 8.6, NH); 9.60 (*s*, H–N(2)). ^{13}C-NMR ((D_6)DMSO): 19.5; 20.2; 51.2; 53.8; 57.2; 66.0; 128.3; 128.3; 128.8; 137.4; 156.5; 171.5. ESI-MS: 278 ($[M+H]^+$). HR-ESI-MS: 278.1499 ($[M+H]^+$, $C_{14}H_{19}N_3O_3^+$; calc. 278.1499). Anal. calc. for $C_{14}H_{19}N_3O_3$ (277.32): C 60.63, H 6.91, N 15.15; found: C 60.60, H 7.06, N 15.09.

8.2. *Benzyl [(4*RS*,5*RS*)-1-Butyl-3-oxo-5-(propan-2-yl)pyrazolidin-4-yl]carbamate* (**10b**). Prepared from **5c** (0.277 g, 1 mmol), **6b** (0.108 ml, 1.2 mmol), and $NaBH_3CN$ (0.150 g, 2.4 mmol); r.t. for 100 h; *GP 4B* (AcOEt/hexanes 1:1). Yield: 67 g (21%). Pale-yellow solid. M.p. 129–133°. IR (KBr): 3549, 3418, 3318, 3161, 3039, 2963, 2935, 2872, 1725, 1690, 1616, 1540, 1456, 1294, 1246, 1054, 777, 732, 694, 668. ^{1}H-NMR ((D_6)DMSO): 0.85, 0.90 (2*d*, 1:1, *J* = 6.5, *Me*$_3$CH); 0.88 (*t*, *J* = 7.1, *Me*CH_2); 1.20–1.49 (*m*, 2 CH_2); 1.79 (*sept.*, *J* = 6.5, Me_2CH); 2.55–2.75 (*m*, CH_2); 2.63 (*dd*, *J* = 5.3, 7.6, H–C(5)); 3.92 (*t*, *J* = 8.3, H–C(4)); 5.05 (*s*, CH_2); 7.29–7.40 (*m*, 5 arom. H); 7.84 (*d*, *J* = 8.8, HN–C(4)); 9.63 (*s*, H–N(2)). ^{13}C-NMR ((D_6)DMSO): 17.0; 18.2; 18.4; 20.2; 29.6; 30.6; 36.6; 54.8; 67.2; 74.6; 128.2; 128.3; 128.6; 136.2; 145.6; 156.0. ESI-MS: 334 ($[M+H]^+$). HR-ESI-MS: 334.2131 ($[M+H]^+$, $C_{18}H_{28}N_3O_3^+$; calc. 334.2131). Anal. calc. for $C_{18}H_{27}N_3O_3 \cdot 1/5\ H_2O$ (297.03): C 64.15, H 8.19, N 12.47; found: C 64.13, H 8.19, N 12.53.

8.3. *Benzyl [(4*RS*,5*RS*)-1-(2-Methylpropyl)-3-oxo-5-(propan-2-yl)pyrazolidin-4-yl]carbamate* (**10c**). Prepared from **5c** (0.277 g, 1 mmol), **6c** (0.108 ml, 1.2 mmol), and $NaBH_3CN$ (0.150 g, 2.4 mmol); r.t. for 24 h; *GP 4B* (AcOEt/hexanes 1:1). Yield: 160 mg (48%). Pale-yellow solid. M.p. 168–172°. IR (KBr): 3465, 3412, 3314, 3154, 3036, 2963, 2933, 2877, 1726, 1684, 1615, 1543, 1469, 1458, 1389, 1295, 1286,

1248, 1052, 778, 739, 730, 694. ^{1}H-NMR ((D$_6$)DMSO): 0.82, 0.87, 0.89, 0.91 (4*d*, 1:1:1:1, *J* = 6.7, 12 H, ^{i}Pr, ^{i}Bu); 1.72–1.85 (*m*, 2 H, ^{i}Pr, ^{i}Bu); 2.30 (*dd*, *J* = 10.7, 11.8, 1 H, CH$_2$); 2.48 (*dd*, *J* = 4.1, 11.8, 1 H, CH$_2$); 2.61 (*dd*, *J* = 5.3, 7.9, H–C(5)); 3.94 (*t*, *J* = 8.4, H–C(4)); 5.05 (*s*, CH$_2$); 7.28–7.40 (*m*, 5 arom. H); 7.87 (*d*, *J* = 8.9, NH); 9.69 (*s*, H–N(2)). ^{13}C-NMR ((D$_6$)DMSO): 17.4; 18.4; 20.3; 20.7; 25.7; 29.6; 53.3; 65.5; 68.2; 73.2; 127.8; 127.9; 128.4; 137.0; 155.8; 168.9. ESI-MS: 334 ([*M* + H]$^+$). HR-ESI-MS: 334.2125 ([*M* + H]$^+$, $C_{18}H_{28}N_3O_3^+$; calc. 334.2131).

8.4. *Benzyl [(4*RS*,5*RS*)-3-Oxo-1,5-di(propan-2-yl)pyrazolidin-4-yl]carbamate* (**10d**). Prepared from **5c** (0.554 g, 2 mmol), **6d** (2 ml), and $NaBH_3CN$ (0.150 g, 2.4 mmol); r.t. for 24 h; *GP 4A*. Yield: 136 g (92%). Brownish solid. M.p. 171–176°. IR (KBr): 3413, 3363, 2968, 3183, 3180, 3082, 3070, 3058, 3035, 2968, 2937, 2929, 2900, 2873, 1711, 1690, 1632, 1617, 1524, 1469, 1456, 1389, 1373, 1339, 1284, 1263, 1235, 1049, 1036, 774, 755, 748, 700, 617, 608, 600. ^{1}H-NMR ((D$_6$)DMSO): 0.86, 0.89, 0.95, 0.99 (4*d*, 1:1:1:1, *J* = 6.5, 2 *Me*$_2$CH); 1.74, 2.89 (2*sept.*, 1:1, *J* = 6.5, 2 Me$_2$C*H*); 2.82 (*t*, *J* = 5.8, H–C(5)); 3.90 (*dd*, *J* = 6.1, 8.6, H–C(4)); 5.03, 5.07 (2*d*, 1:1, *J* = 12.7, CH$_2$); 7.30–7.39 (*m*, 5 arom. H); 7.92 (*d*, *J* = 8.6, NH); 9.56 (*s*, H–N(2)). ^{13}C-NMR ((D$_6$)DMSO): 17.3; 17.4; 18.3; 20.9; 30.7; 53.5; 55.4; 65.5; 69.4; 127.7; 127.9; 128.4; 137.0; 155.8; 168.7. ESI-MS: 320 ([*M* + H]$^+$). HR-ESI-MS: 320.1983 ([*M* + H]$^+$, $C_{17}H_{26}N_3O_3^+$; calc. 320.1974). Anal. calc. for $C_{17}H_{25}N_3O_3 \cdot H_2O$ (337.41): C 60.51, H 8.07, N 12.45; found: C 60.44, H 7.61, N 12.77.

8.5. *Benzyl [(4*RS*,5*RS*)-1-Benzyl-3-oxo-5-(propan-2-yl)pyrazolidin-4-yl]carbamate* (**10e**). Prepared from **5c** (0.277 g, 1 mmol), **6f** (0.122 ml, 1.2 mmol), and $NaBH_4$ (75 mg, 1.2 mmol); r.t. for 12 h; *GP 4B* (AcOEt/hexanes 3:1). Yield: 207 mg (56%). White solid. For physical, anal., and spectroscopic data for **10e**, see above.

8.6. *Benzyl [(4*RS*)-1-Benzyl-5,5-dimethyl-3-oxopyrazolidin-4-yl]carbamate* (**10f**). Prepared from **5d** (0.263 g, 1 mmol), **6f** (0.122 ml, 1.2 mmol), and $NaBH_4$ (38 mg, 1.2 mmol); r.t. for 24 h; *GP 4B*, first FC, then MPLC (AcOEt/hexanes 3:1). Yield: 186 mg (53%). White solid. M.p. 116–120°. IR (KBr): 3406, 3318, 3059, 3033, 2972, 1717, 1698, 1541, 1454, 1371, 1353, 1282, 1253, 1092, 1081, 1062, 1022, 730, 698, 668. ^{1}H-NMR ((D$_6$)DMSO): 1.02, 1.20 (2*s*, 1:1, 2 Me); 3.88 (*s*, CH$_2$); 4.42 (*d*, *J* = 9.3, H–C(4)); 5.06, 5.11 (2*d*, 1:1, *J* = 12.5, CH$_2$); 7.23–7.39 (*m*, 10 arom. H); 7.66 (*d*, *J* = 9.3, HN–C(4)); 9.40 (*s*, H–N(2)). ^{13}C-NMR ((D$_6$)DMSO): 19.8; 23.5; 56.0; 59.1; 65.3; 65.7; 126.9; 127.8; 127.9; 128.1; 128.4; 128.8; 136.9; 138.2; 156.8; 171.1. ESI-MS: 354 ([*M* + H]$^+$). HR-ESI-MS: 354.1808 ([*M* + H]$^+$, $C_{20}H_{24}N_3O_3^+$; calc. 354.1818). Anal. calc. for $C_{20}H_{23}N_3O_3$ (353.41): C 67.97, H 6.56, N 11.89; found: C 67.96, H 6.26, N 11.85.

8.7. *Benzyl [(4*RS*,5*RS*)-1-Butyl-3-oxo-5-phenylpyrazolidin-4-yl]carbamate* (**10g**). Prepared from **5f** (311 mg, 1 mmol), **6b** (0.108 ml, 1.2 mmol), and $NaBH_3CN$ (150 mg, 2.4 mmol); reflux for 3 h; *GP 4B* (AcOEt/hexanes 1:1). Yield: 232 mg (63%). White solid. M.p. 136–140°. IR (KBr): 3450, 3335, 3063, 3036, 2950, 2869, 2843, 1713, 1688, 1533, 1497, 1468, 1455, 1381, 1358, 1312, 1253, 1078, 1050, 784, 456, 706, 697. ^{1}H-NMR ((D$_6$)DMSO): 0.75 (*t*, *J* = 7.3, Me); 1.15, 1.26 (2*tq*, 1:1, *J* = 7.4, 7.4, CH$_2$); 1.40 (*tt*, *J* = 7.2, 7.2, CH$_2$); 2.39 (*td*, *J* = 7.3, 12.5, 1 H, CH$_2$); 2.55 (*td*, *J* = 8.1, 12.5, 1 H, CH$_2$); 3.75 (*d*, *J* = 11.4, H–C(5)); 4.11 (*dd*, *J* = 9.0, 11.4, H–C(4)); 4.97, 5.00 (2*d*, 1:1, *J* = 12.7, 1 H, CH$_2$); 7.26–7.40 (*m*, 10 arom. H); 7.85 (*d*, *J* = 9.0, NH); 9.92 (*s*, H–N(2)). ^{13}C-NMR ((D$_6$)DMSO): 13.6; 19.6; 28.5; 30.7; 57.4; 65.5; 72.0; 127.6; 127.7; 127.8; 128.0; 128.4; 128.6; 136.9; 138.3; 155.9; 168.2. ESI-MS: 368 ([*M* + H]$^+$). HR-ESI-MS: 368.1960 ([*M* + H]$^+$, $C_{21}H_{26}N_3O_3^+$; calc. 368.1974). Anal. calc. for $C_{21}H_{25}N_3O_3$ (367.44): C 68.64, H 6.86, N 11.44; found: C 68.57, H 6.95, N 11.40.

8.8. *Benzyl [(4*RS*,5*RS*)-1-(2-Methylpropyl)-3-oxo-5-phenylpyrazolidin-4-yl]carbamate* (**10h**). Prepared from **5f** (311 mg, 1 mmol), **6b** (0.091 ml, 1.2 mmol), and $NaBH_3CN$ (150 mg, 2.4 mmol); reflux for 5 h; *GP 4B* (AcOEt/hexanes 1:1). Yield: 289 mg (78%). White solid. M.p. 140–145°. IR (KBr): 3458, 3279, 3258, 3154, 3036, 2959, 2932, 2872, 2831, 1724, 1691, 1545, 1497, 1454, 1387, 1365, 1260, 1180, 1060, 758, 735, 701. ^{1}H-NMR ((D$_6$)DMSO): 0.73, 0.81 (2*d*, 1:1, *J* = 6.8, 2 Me); 0.95 (*m*, 1 H, ^{i}Bu); 2.17 (*dd*, *J* = 10.6, 11.9, 1 H, ^{i}Bu); 2.30 (*dd*, *J* = 4.3, 11.9, 1 H, ^{i}Bu); 3.73 (*d*, *J* = 11.4, H–C(5)); 4.08 (*dd*, *J* = 9.0, 11.4, H–C(4)); 4.97, 4.99 (2*d*, 1:1, *J* = 12.7, CH$_2$); 7.26–7.41 (*m*, 10 arom. H); 7.86 (*d*, *J* = 9.0, NH); 9.94 (*s*, H–N(2)). ^{13}C-NMR ((D$_6$)DMSO): 20.3; 20.6; 25.4; 60.0; 65.5; 66.1; 72.2; 127.6; 127.7; 127.8; 128.2; 128.4; 128.6; 136.9; 138.2; 155.9; 168.3. ESI-MS: 368 ([*M* + H]$^+$). HR-ESI-MS: 368.1964 ([*M* + H]$^+$, $C_{21}H_{26}N_3O_3^+$; calc. 368.1974).

8.9. *Benzyl [(4*RS*,5*RS*)-3-Oxo-5-phenyl-1-(propan-2-yl)pyrazolidin-4-yl]carbamate* (**10i**). Prepared from **5f** (311 mg, 1 mmol), **6d** (1 ml), and $NaBH_3CN$ (150 mg, 2.4 mmol); reflux for 24 h; *GP 4A*. Yield:

74 mg (21%). White solid. M.p. 182–186°. IR (KBr): 3475, 3385, 3064, 3038, 2978, 1726, 1698, 1635, 1518, 1454, 1391, 1376, 1346, 1285, 1230, 1199, 1155, 1038, 752, 699, 635, 546. ^{1}H-NMR ((D$_6$)DMSO): 0.95, 0.96 (2*d*, 1:1, *J* = 6.5, 2 Me); 2.76 (*sept.*, *J* = 6.5, Me$_2$C*H*); 3.99–4.04 (*m*, H–C(4), H–C(5)); 5.00 (*s*, CH$_2$); 7.30–7.41 (*m*, 10 arom. H); 7.88 (*dd*, *J* = 8.3, NH); 9.73 (*s*, H–N(2)). ^{13}C-NMR ((D$_6$)DMSO): 15.6; 20.6; 53.5; 60.5; 65.5; 67.6; 127.3; 127.6; 127.8; 127.8; 128.4; 128.6; 136.9; 139.8; 155.9; 167.5. ESI-MS: 354 ([*M* + H]$^+$). HR-ESI-MS: 354.1817 ([*M* + H]$^+$, $C_{20}H_{24}N_3O_3^+$; calc. 354.1818). Anal. calc. for $C_{20}H_{23}N_3O_3 \cdot 1/2\,H_2O$ (362.43): C 66.28, H 6.67, N 11.59; found: C 66.20, H 6.36, N 11.53.

8.10. *Benzyl [(4*RS*,5*RS*)-1-Benzyl-3-oxo-5-phenylpyrazolidin-4-yl]carbamate* (**10j**). Prepared from **5f** (1.555 g, 5 mmol), **6f** (0.610 ml, 6 mmol), and NaBH$_4$ (0.190 g, 5 mmol); r.t. for 2 h; *GP 4B* (AcOEt). Yield: 1.91 g (95%). White solid. M.p. 178–182°. IR (KBr): 3442, 3331, 1717, 1691, 1539, 1497, 1455, 1352, 1352, 1254, 1057, 756, 696. ^{1}H-NMR ((D$_6$)DMSO): 3.60, 3.89 (2*d*, 1:1, *J* = 13.9, CH$_2$); 3.93 (*d*, *J* = 10.7, H–C(5)); 4.16 (*dd*, *J* = 9.2, 10.7, H–C(4)); 4.99 (*s*, CH$_2$); 6.90–7.50 (*m*, 15 arom. H); 7.93 (*d*, *J* = 9.2, NH); 9.86 (*s*, H–N(2)). ^{13}C-NMR ((D$_6$)DMSO): 59.9; 60.0; 65.5; 70.4; 127.4; 127.6; 127.6; 127.8; 128.1; 128.3; 128.4; 128.6; 129.3; 135.7; 136.9; 137.9; 156.0; 168.2. ESI-MS: 402 ([*M* + H]$^+$). HR-ESI-MS: 402.1805 ([*M* + H]$^+$, $C_{24}H_{24}N_3O_3^+$; calc. 402.1818). Anal. calc. for $C_{24}H_{23}N_3O_3$ (401.46): C 71.80, H 5.77, N 10.47; found: C 71.60, H 5.51, N 10.72.

9. *General Procedure for the Synthesis of 1,2,5-Trisubstituted (4*RS*,5*RS*)-4-{[(Benzyloxy)carbonyl]-amino}pyrazolidin-3-ones* **12** (*GP 5*). A mixture of **10** (1 mmol), anh. DMF (5 ml), K_2CO_3 (138 mg, 1 mmol), and **11** (1–8 mmol) was stirred under Ar for 24–96 h. Volatile components were evaporated *in vacuo*, and the residue was purified by CC (AcOEt/hexanes). Fractions containing the product were combined and evaporated *in vacuo* to give **12**.

9.1. *Benzyl [(3*RS*,4*RS*)-1-Methyl-5-oxo-2,3-di(propan-2-yl)pyrazolidin-4-yl]carbamate* (**12a**). Prepared from **10d** (319 mg, 1 mmol) and **11a** (227 µl, 3.3 mmol); 96 h; CC (AcOEt/hexanes 1:2). Yield: 204 mg (61%). Pale-yellow solid. M.p. 107–111°. IR (KBr): 3243, 3063, 3035, 2978, 2964, 2928, 2892, 2873, 1709, 1665, 1587, 1526, 1487, 1456, 1430, 1402, 1386, 1378, 1362, 1349, 1339, 1301, 1258, 1214, 1156, 1134, 1111, 1096, 1082, 1056, 1017, 996, 972, 960, 916, 903, 861, 837, 791, 779, 761, 737, 701, 663. ^{1}H-NMR ((D$_6$)DMSO): 0.88–0.99 (*m*, 3 Me); 1.09 (*d*, *J* = 6.7, Me); 1.78–1.88 (*m*, Me$_2$C*H*); 2.96 (br. *s*, H–C(3)); 3.00 (*s*, Me–C(1)); 3.25 (*sept.*, *J* = 6.7, Me$_2$C*H*); 4.11 (*d*, *J* = 2.9, H–C(4)); 5.09, 5.15 (2*d*, 1:1, *J* = 12.1, CH$_2$); 5.11 (br. *s*, NH, overlapped by the signal for CH$_2$); 7.30–7.39 (*m*, 5 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 17.1; 17.2; 18.5; 20.0; 31.4; 33.2; 52.6; 55.7; 65.5; 67.2; 128.3; 128.3; 128.6; 136.2; 156.1; 168.2. ESI-MS: 334 ([*M* + H]$^+$). HR-ESI-MS: 334.2125 ([*M* + H]$^+$, $C_{18}H_{28}N_3O_3^+$; calc. 334.2125). Anal. calc. for $C_{18}H_{27}N_3O_3$ (333.21): C 64.84, H 8.16, N 12.60; found: C 65.05, H 8.42, N 12.60.

9.2. *Benzyl [(3*RS*,4*RS*)-1-Benzyl-5-oxo-2,3-di(propan-2-yl)pyrazolidin-4-yl]carbamate* (**12b**). Prepared from **10d** (319 mg, 1 mmol) and **11b** (119 µl, 1.3 mmol); 72 h; CC (AcOEt/hexanes 1:2). Yield: 182 mg (45%). Yellow solid. M.p. 112–115°. IR (KBr): 3235, 3090, 3066, 3036, 2976, 2958, 2890, 2874, 1699, 1662, 1521, 1496, 1448, 1385, 1369, 1346, 1325, 1303, 1264, 1218, 1167, 1160, 1128, 1117, 1098, 1084, 1058, 1046, 1019, 997, 966, 916, 902, 862, 824, 784, 752, 737, 698, 678. ^{1}H-NMR ((D$_6$)DMSO): 0.81, 0.69 (2*d*, 1:1, *J* = 4.7, 2 Me); 0.85, 1.04 (2*d*, 1:1, *J* = 6.6, 2 Me); 1.44–1.57 (*m*, Me$_2$C*H*); 2.81 (*d*, *J* = 5.0, H–C(3)); 3.26 (*sept.*, *J* = 6.4, Me$_2$C*H*); 4.16 (*d*, *J* = 5.0, H–C(4)); 4.34, 4.78 (2*d*, 1:1, *J* = 14.7, CH$_2$); 5.09, 5.16 (2*d*, 1:1, *J* = 12.0, CH$_2$); 5.16 (br. *s*, NH); 7.27–7.40 (*m*, 10 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 16.5; 18.1; 18.3; 20.3; 32.8; 48.0; 52.0; 55.7; 65.1; 67.4; 128.0; 128.5; 128.5; 128.5; 128.7; 129.2; 136.2; 136.2; 156.0; 168.4. ESI-MS: 410 ([*M* + H]$^+$). HR-ESI-MS: 410.2438 ([*M* + H]$^+$, $C_{24}H_{32}N_3O_3^+$; calc. 410.2438). Anal. calc. for $C_{24}H_{31}N_3O_3$ (409.52): C 70.39, H 7.63, N 10.26; found: C 70.39, H 7.85, N 10.25.

9.3. *Ethyl [(3*RS*,4*RS*)-4-{[(Benzyloxy)carbonyl]amino}-5-oxo-2,3-di(propan-2-yl)pyrazolidin-1-yl]acetate* (**12c**). Prepared from **10d** (319 mg, 1 mmol) and **11c** (118 µl, 1.3 mmol); 48 h; CC (AcOEt/hexanes 1:2). Yield: 307 mg (76%). Colorless semisolid. M.p. 81–83°. IR (KBr): 3302, 3053, 3032, 2970, 2906, 2863, 1745, 1720, 1677, 1535, 1474, 1455, 1435, 1417, 1383, 1372, 1328, 1291, 1233, 1196, 1179, 1149, 1120, 1107, 1072, 1051, 1027, 989, 965, 949, 933, 909, 874, 856, 842, 801, 777, 757, 734, 705, 654. ^{1}H-NMR ((D$_6$)DMSO): 0.95 (*d*, *J* = 5.4, Me); 0.98–1.04 (*m*, 2 Me); 1.08 (*d*, *J* = 6.8, Me); 1.27 (*t*, *J* = 7.2, *Me*CH$_2$); 1.80–1.90 (*m*, Me$_2$C*H*); 2.87 (*d*, *J* = 3.2, H–C(3)); 3.16 (*sept.*, *J* = 6.5, Me$_2$C*H*); 4.05, 4.23 (2*d*, 1:1, *J* = 17.0, CH$_2$); 4.13–4.26 (*m*, MeC*H*$_2$, H–C(4)); 5.10, 5.16 (2*d*, 1:1, *J* = 12.1, CH$_2$); 5.22 (br. *s*, NH); 7.30–7.44 (*m*, 5 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 14.3; 17.3; 18.6; 18.7; 20.2; 32.6; 47.1; 53.6; 55.4; 61.8; 66.6; 67.5; 128.4; 128.5; 128.8; 136.1; 155.9; 167.7; 169.5. ESI-MS: 406 ([*M* + H]$^+$). HR-ESI-MS: 406.2336

([$M+H$]$^+$, $C_{21}H_{32}N_3O_5^+$; calc. 406.2336). Anal. calc. for $C_{21}H_{31}N_3O_5$ (405.49): C 62.20, H 7.71, N 10.36); found: C 62.36, H 7.76, N 10.46.

9.4. tert-*Butyl [(3*RS*,4*RS*)-4-{[(Benzyloxy)carbonyl]amino}-5-oxo-2,3-di(propan-2-yl)pyrazolidin-1-yl]acetate* (**12d**). Prepared from **10d** (319 mg, 1 mmol) and **11d** (192 µl, 1.3 mmol); 48 h; CC (AcOEt/hexanes 1:2). Yield: 228 mg (53%). Colorless oil. IR (NaCl): 3282, 3034, 2971, 2936, 2875, 1720, 1678, 1530, 1455, 1390, 1368, 1334, 1298, 1249, 1222, 1152, 1046, 1027, 982, 941, 920, 846, 803, 774, 752, 735, 697. ^{1}H-NMR ((D$_6$)DMSO): 0.94 (*d*, *J* = 5.3, Me); 1.01 (*d*, *J* = 6.4, 2 Me); 1.08 (*d*, *J* = 6.8, Me); 1.46 (*s*, *t*-Bu); 1.81–1.90 (*m*, Me$_2$C*H*); 2.85 (*d*, *J* = 4.9, H–C(3)); 3.15 (*sept.*, *J* = 6.7, Me$_2$C*H*); 3.95, 4.12 (2*d*, 1:1, *J* = 16.8, CH$_2$); 4.21 (*d*, *J* = 4.9, H–C(4)); 5.09, 5.15 (2*d*, 1:1, *J* = 12.2, CH$_2$); 5.28 (*d*, *J* = 6.6, NH); 7.30–7.38 (*m*, 5 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 17.5; 18.6; 18.7; 20.1; 28.2; 32.5; 48.0; 53.6; 55.5; 66.6; 67.4; 82.5; 128.4; 128.4; 128.7; 136.2; 155.9; 166.7; 169.3. ESI-MS: 434 ([$M+H$]$^+$). HR-ESI-MS: 434.2647 ([$M+H$]$^+$, $C_{23}H_{36}N_3O_5^+$; calc. 434.2649).

9.5. *Benzyl [(4*RS*,5*RS*)-1-Benzyl-2-methyl-3-oxo-5-(propan-2-yl)pyrazolidin-4-yl]carbamate* (**12e**). Prepared from **10e** (928 mg, 2.5 mmol) and **11a** (568 µl, 8.25 mmol); 72 h; CC (AcOEt/hexanes 1:1). Yield: 661 mg (70%). White solid. M.p. 113–115°. IR (KBr): 3230, 3052, 3031, 3009, 2964, 2950, 2931, 2894, 2872, 1707, 1660, 1586, 1544, 1496, 1458, 1389, 1365, 1351, 1324, 1305, 1271, 1245, 1217, 1177, 1159, 1136, 1111, 1095, 1083, 1043, 1026, 1002, 991, 979, 919, 863, 820, 808, 767, 751, 719, 700, 646, 620. ^{1}H-NMR ((D$_6$)DMSO): 0.80–0.94 (*m*, 2 Me); 1.65–1.82 (*m*, Me$_2$C*H*); 2.95 (*dd*, *J* = 2.5, 5.2, H–C(5)); 3.07 (*s*, Me–C(2)); 3.89, 4.05 (2*d*, 1:1, CH$_2$),3.99 (*dd*, *J* = 2.5, 7.5, H–C(4)); 4.12 (*d*, *J* = 7.2, NH); 5.08 (*s*, CH$_2$); 7.18–7.24, 7.30–7.43 (2*m*, 1:4, 10 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 17.4; 18.7; 30.6; 32.1; 55.6; 60.2; 67.1; 69.9; 128.1; 128.3; 128.6; 128.7; 128.9; 130.4; 135.2; 136.4; 155.8; 168.4. ESI-MS: 382 ([$M+H$]$^+$). HR-ESI-MS: 382.2123 ([$M+H$]$^+$, $C_{22}H_{28}N_3O_3^+$; calc. 382.2125). Anal. calc. for $C_{22}H_{27}N_3O_3$ (381.47): C 69.27, H 7.13, N 11.02; found: C 69.40, H 7.35, N 11.25.

9.6. *Benzyl [(4*RS*,5*RS*)-1,2-Dibenzyl-3-oxo-5-(propan-2-yl)pyrazolidin-4-yl]carbamate* (**12f**). Prepared from **10e** (367 mg, 1 mmol) and **11b** (119 µl, 1 mmol); 72 h; CC (AcOEt/hexanes 1:3). Yield: 334 mg (73%). White solid. M.p. 150–153°. IR (KBr): 3249, 3083, 3061, 3029, 3010, 2974, 2947, 2923, 2891, 2868, 1956, 1725, 1657, 1542, 1495, 1454, 1422, 1384, 1367, 1344, 1319, 1238, 1176, 1157, 1137, 1120, 1085, 1049, 1028, 1008, 989, 970, 958, 938, 913, 868, 846, 812, 766, 751, 730, 700, 666, 617. ^{1}H-NMR ((D$_6$)DMSO): 0.50 (*d*, *J* = 4.8, Me); 0.72 (br. *s*, Me); 1.29–1.40 (*m*, Me$_2$C*H*); 2.79 (*d*, *J* = 7.2, H–C(5)); 3.91, 3.97 (2*d*, 1:1, *J* = 13.2, CH$_2$); 3.99 (*d*, *J* = 7.2, H–C(4)); 4.28, 4.97 (2*d*, 1:1, CH$_2$); 4.29 (*s*, HN–C(4)); 5.07 (*s*, CH$_2$); 7.12–7.15, 7.29–7.44 (2*m*, 1:14, 15 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 18.3; 18.5; 31.3; 47.3; 55.9; 60.8; 67.1; 70.5; 128.1; 128.2; 28.3; 128.4; 128.6; 128.7; 128.8; 129.3; 130.4; 135.4; 136.1; 136.4; 155.8; 168.8. ESI-MS: 458 ([$M+H$]$^+$). HR-ESI-MS: 458.2435 ([$M+H$]$^+$, $C_{28}H_{32}N_3O_3^+$; 458.2438). Anal. calc. for $C_{28}H_{31}N_3O_3$ (457.24): C 73.50, H 6.83, N 9.18; found: C 73.32, H 7.02, N 9.20.

9.7. *Ethyl [(3*RS*,4*RS*)-2-Benzyl-4-{[(benzyloxy)carbonyl]amino}-5-oxo-3-(propan-2-yl)pyrazolidin-1-yl]acetate* (**12g**). Prepared from **10e** (367 mg, 1 mmol) and **11c** (118 µl, 1.3 mmol); 24 h; CC (AcOEt/hexanes 1:3). Yield: 437 mg (97%). Colorless semisolid. IR (KBr): 3216, 3049, 3025, 2995, 2975, 2958, 2940, 2873, 1756, 1728, 1665, 1604, 1549, 1496, 1480, 1455, 1430, 1392, 1371, 1347, 1248 1201, 1159, 1134, 1119, 1069, 1045, 1026, 989, 970, 954, 939, 926, 903, 863, 847, 816, 769, 732, 697, 679. ^{1}H-NMR ((D$_6$)DMSO): 0.89 (*d*, *J* = 5.8, Me); 0.94 (br. *s*, Me); 1.25 (*t*, *J* = 7.1, *Me*CH$_2$); 1.76–1.87 (*m*, Me$_2$C*H*); 2.88 (br. *s*, H–C(3)); 3.87, 4.30 (2*d*, 1:1, *J* = 17.0, CH$_2$); 3.95, 4.01 (2*d*, 1:1, *J* = 13.4, CH$_2$); 4.10–4.20 (*m*, MeC*H*$_2$, H–C(4)); 4.53 (br. *s*, NH); 5.09 (*s*, CH$_2$); 7.23–7.28, 7.30–7.40 (2*m*, 1:4, 10 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 14.3; 18.6; 19.1; 31.1; 46.3; 55.3; 61.6; 61.8; 67.2; 71.9; 128.2; 128.4; 128.5; 128.7; 128.9; 130.1; 135.7; 136.3; 155.8; 167.6; 170.0. ESI-MS: 454 ([$M+H$]$^+$). HR-ESI-MS: 454.2337 ([$M+H$]$^+$, $C_{25}H_{32}N_3O_5^+$; calc. 454.2336). Anal. calc. for $C_{25}H_{31}N_3O_5$ (453.53): C 66.21, H 6.89, N 9.27; found: C 66.23, H 7.13, N 9.18.

9.8. *Benzyl [(4*RS*,5*RS*)-1-Benzyl-2-methyl-3-oxo-5-phenylpyrazolidin-4-yl]carbamate* (**12h**). Prepared from **10j** (402 mg, 1 mmol) and **11a** (227 µl, 3.3 mmol), 48 h, CC: AcOEt/hexanes 1:3. Yield: 210 mg (50%). Colorless oil. IR (NaCl): 3291, 3060, 3030, 2923, 2853, 2154, 1682, 1605, 1538, 1496, 1481, 1454, 1425, 1397, 1369, 1344, 1293, 1253, 1210, 1189, 1106, 1056, 1029, 993, 916, 872, 780, 752, 730, 713, 696, 659. ^{1}H-NMR ((D$_6$)DMSO): 3.05 (*s*, Me); 3.98, 4.09 (2*d*, 1:1, *J* = 14.4, CH$_2$); 4.20 (br. *s*, H–C(5)); 4.26 (br. *t*, *J* = 7.3, H–C(4)); 4.98 (br. *s*, NH); 5.08 (*s*, CH$_2$); 7.22–7.38, 7.44–7.48 (2*m*, 13:2, 15 H, Ph). ^{13}C-NMR ((D$_6$)DMSO): 31.9; 59.5; 60.6; 67.4; 69.5; 127.4; 128.2; 128.3; 128.3; 128.4; 128.7; 128.8; 128.9;

129.3; 136.1; 136.2; 138.4; 156.1; 167.5. ESI-MS: 416 ($[M+H]^+$). HR-ESI-MS: 416.1966 ($[M+H]^+$, $C_{25}H_{26}N_3O_3^+$; calc. 416.1969).

10. *General Procedure for Preparation of Amines* **13**–**15** (*GP 6*). A mixture of **5**, **10**, or **12** (1 mmol), EtOH (20 ml), and 10% Pd/C (50–100 mg) was hydrogenated (3.5 bar of H_2) at r.t. for 1–17 h. The catalyst was removed by filtration, washed with EtOH (2 × 5 ml), and the combined filtrate was evaporated *in vacuo* to give **13**, **14**, or **15**, resp.

10.1. *(4*RS,*5*RS*)-4-Amino-5-(propan-2-yl)pyrazolidin-3-one* (**13**). Prepared from **5c** (1.37 g, 4.95 mmol), EtOH (50 ml), and 10% Pd/C (200 mg); 2.5 h. Yield: 707 mg (100%). White solid. M.p. 118–122°. IR (KBr): 3355, 3283, 2966, 2872, 2858, 1726, 1684, 1601, 1507, 1471, 1385, 1334, 1311, 1213, 1174, 1112, 1042, 983, 962, 947, 910, 869, 846, 712, 668. ^{1}H-NMR ((D_6)DMSO): 0.90, 0.97 (2*d*, 1:1, *J* = 6.8, 2 Me); 1.75 (*sept.*, *J* = 6.8, Me_2CH); 2.64 (*t*, *J* = 8.7, H–C(5)); 3.10 (*d*, *J* = 9.7, H–C(4)); 3.34 (br. *s*, NH_2); 4.84 (br. *s*, H–N(1)); 9.12 (*s*, H–N(2)).^{13}C-NMR ((D_6)DMSO): 19.5; 19.5; 30.3; 56.5; 71.9; 177.2. ESI-MS: 144 ($[M+H]^+$). HR-ESI-MS: 144.1133 ($[M+H]^+$, $C_6H_{14}N_3O^+$; calc. 144.1059). Anal. calc. for $C_6H_{13}N_3O$ (143.19): C 50.33, H 9.15, N 29.35; found: C 50.37, H 8.94, N 25.52.

10.2. *(4*RS,*5*RS*)-4-Amino-1,5-di(propan-2-yl)pyrazolidin-3-one* (**14a**). Prepared from **10d** (500 mg, 1.57 mmol), EtOH (40 ml), 10% Pd/C (90 mg), 3.5 h. Yield: 289 mg (100%). Brown semisolid. IR(NaCl): 3367, 3348, 3286, 3140, 2966, 2934, 2871, 1669, 1461, 1387, 1368, 1343, 1329, 1180, 1154, 1126, 1086, 1062, 1026, 956, 938, 922, 891, 865, 846, 826, 793, 713, 656. ^{1}H-NMR ($CDCl_3$): 0.95, 0.97 (2*d*, 1:1, *J* = 7.0, 2 Me); 1.08, 1.12 (2*d*, 1:1, *J* = 6.4, 2 Me); 1.67 (br. *s*, NH_2); 1.78 (*sept.*, *J* = 6.9, Me_2CH); 2.78 (*dd*, *J* = 4.3, 5.8, H–C(5)); 2.94 (*sept.*, *J* = 6.3, Me_2CH); 3.27 (*d*, *J* = 4.2, H–C(4)); 8.18 (br. *s*, H–N(2)). ^{13}C-NMR ($CDCl_3$): 17.7; 18.0; 18.6; 20.9; 32.2; 55.8; 57.3; 72.5; 174.4. ESI-MS: 186 ($[M+H]^+$). HR-ESI-MS: 186.1601 ($[M+H]^+$, $C_9H_{20}N_3O^+$; calc. 186.1601).

10.3. *(4*RS,*5*RS*)-4-Amino-1-benzyl-5-(propan-2-yl)pyrazolidin-3-one* (**14b**). Prepared from **10e** (205 mg, 0.56 mmol), EtOH (20 ml), 10% Pd/C (10 mg); 17 h. Yield: 105 mg (90%). Brown oil. IR (NaCl): 3025, 2960, 2931, 2895, 2868, 1681, 1602, 1588, 1575, 1494, 1467, 1455, 1434, 1393, 1382, 1366, 1349, 1317, 1303, 1262, 1179, 1134, 1082, 1066, 1029, 975, 899, 854, 833, 740, 698, 643. ^{1}H-NMR ((D_6)DMSO): 0.79, 0.81 (2*d*, 1:1, *J* = 6.9, 2 Me); 1.62 (*sept.*, *J* = 6.6, Me_2CH); 2.62 (*t*, *J* = 5.3, H–C(5)); 3.04 (*d*, *J* = 5.0, H–C(4)); 3.83, 3.96 (2*d*, *J* = 13.0, CH_2); 7.22–7.40 (*m*, 5 arom. H); 9.40 (*s*, H–N(2)); NH_2 exchanged. ^{13}C-NMR ($CDCl_3$): 18.4; 18.8; 30.6; 55.4; 64.7; 75.7; 128.2; 128.8; 129.6; 136.2; 173.6. ESI-MS: 234 ($[M+H]^+$). HR-ESI-MS: 234.16 ($[M+H]^+$, $C_{13}H_{20}N_3O^+$; calc. 234.1601).

10.4. *(4*RS,*5*RS*)-4-Amino-1-benzyl-2-methyl-5-(propan-2-yl)pyrazolidin-3-one* (**15a**). Prepared from **12e** (551 mg, 1.44 mmol), EtOH (20 ml), 10% Pd/C (100 mg), 1 h. Yield: 345 mg (97%). Brown oil. IR (NaCl): 3360, 3293, 3087, 3062, 3031, 2985, 2931, 2872, 1667, 1603, 1495, 1466, 1454, 1427, 1394, 1365, 1297, 1261, 1205, 1066, 1028, 1005, 971, 916, 880, 842, 795, 754, 726, 699, 636. ^{1}H-NMR ((D_6)DMSO): 0.83, 0.84 (2*d*, 1:1, *J* = 6.7, 2 Me); 1.45 (br. *s*, NH_2); 1.60–1.69 (*dsept.*, *J* = 1.3, 6.6, Me_2CH); 2.77 (*dd*, *J* = 2.8, 5.5, H–C(5)); 3.03 (*s*, Me); 3.16 (*d*, *J* = 2.8, H–C(4)); 3.98, 4.09 (2*d*, 1:1, *J* = 13.4, CH_2); 7.28–7.43 (*m*, 5 arom. H).^{13}C-NMR ((D_6)DMSO): 17.7; 18.4; 30.5; 32.2; 56.4; 60.6; 71.3; 128.3; 128.8; 130.3; 135.7; 172.4. ESI-MS: 248 ($[M+H]^+$). HR-ESI-MS: 248.1769 ($[M+H]^+$, $C_{14}H_{22}N_3O^+$; calc. 248.1685).

10.5. *(4*RS,*5*RS*)-4-Amino-1-benzyl-2-methyl-5-phenylpyrazolidin-3-one* (**15b**). Prepared from **12h** (100 mg, 0.24 mmol), EtOH (20 ml), 10% Pd/C (10 mg); 1 h. Yield: 63 mg (94%). Purple oil. IR (NaCl): 3369, 3304, 3086, 3062, 3030, 3006, 2922, 2860, 1685, 1602, 1495, 1475, 1454, 1423, 1394, 1365, 1305, 1285, 1250, 1199, 1157, 1096, 1070, 1028, 1002, 967, 909, 851, 790, 729, 698, 643. ^{1}H-NMR ((D_6)DMSO): 1.87 (br. *s*, NH_2); 2.98 (*s*, *J* = 6.8, Me); 3.54 (*d*, *J* = 9.7, H–C(4)); 3.71 (*d*, *J* = 9.7, H–C(5)); 3.83, 4.10 (2*d*, 1:1, *J* = 14.6, CH_2); 7.23–7.45 (*m*, 10 arom. H).^{13}C-NMR ((D_6)DMSO): 32.0; 59.1; 60.7; 73.4; 127.8; 127.8; 128.4; 128.6; 129.0; 129.0; 136.5; 138.4; 170.9. ESI-MS: 282 ($[M+H]^+$). HR-ESI-MS: 282.16 ($[M+H]^+$, $C_{17}H_{20}N_3O^+$; calc. 282.1601).

11. *General Procedure for the Preparation of 1,5-Disubstituted (4*RS,*5*RS*)-4-Alkylaminopyrazolidin-3-ones* **16** (*GP 7*). A mixture of **10** (1 mmol), MeOH (10 ml), carbonyl compound **6** (1 mmol), 1M aq. HCl (2 drops), and 10% Pd/C (30 mg) was hydrogenated (3.5 bar of H_2) at r.t. 4–13 h. The catalyst was removed by filtration, washed with MeOH (2 × 5 ml), and the combined filtrate was evaporated *in vacuo* to give **16**.

11.1. *(4*RS*)-1-(Propan-2-yl)-4-(propan-2-ylamino)pyrazolidin-3-one* (**16a**). Prepared from **10a** (277mg, 1 mmol) and **6** [4] (10 ml, excess), 5 h. Yield: 185 mg (100%). Reddish solid. M.p. 60–64°. IR (KBr): 3418, 2973, 2834, 1694, 1470, 1387, 1338, 1179, 1065, 1014, 901, 838, 771, 657. ^{1}H-NMR ($CDCl_3$): 0.97, 0.99, 1.00, 1.02 (4*d*, 1:1:1:1, *J* = 6.4, 4 Me); 1.91 (*s*, NH); 2.73 (br. *s*, H_a–C(5)); 2.89–2.98 (*sept.*, *J* = 6.4, Me_2CH); 3.16 (*s*, H_b–C(5)); 3.52 (*dd*, *J* = 10.5, 7.9, H–C(4)); 3.60 (br. *s*, Me_2CH); 9.59 (*s*, H–N(2)). ^{13}C-NMR ($CDCl_3$): 19.3; 20.0; 22.7; 22.9; 48.5; 56.1; 57.5; 57.9; 173.8. ESI-MS: 186 ($[M+H]^+$). HR-ESI-MS: 186.1592 ($[M+H]^+$, $C_9H_{20}N_3O^+$; calc. 186.1601).

11.2. *(4*RS*,5*RS*)-4-(Butylamino)-1,5-di(propan-2-yl)pyrazolidin-3-one* (**16b**). Prepared from **10d** (250 mg, 0.78 mmol) and **6b** (98 µl, 1 mmol), 9 h. Yield: 227 mg (100%). Yellow oil. IR (NaCl): 3176, 2932, 2959, 2873, 1689, 1467, 1385, 1368, 1203, 1166, 1104, 1006, 838, 798, 768, 665. ^{1}H-NMR ((D_6)DMSO): 0.83–0.90 (*m*, Me_2CH, $MeCH_2$); 0.96, 0.98 (2*d*, 1:1, *J* = 6.4, Me_2CH); 1.25–1.42 (*m*, 2 CH_2); 1.56 (*sept.*, Me_2CH); 1.76 (br. *s*, NH); 2.51–2.59, 2.60–2.68 (2*m*, 1:1, CH_2); 2.79 (*dd*, *J* = 2.4, 5.9, H–C(5)); 2.81 (br. *d*, *J* = 2.4, H–C(4)); 2.95 (*sept.*, *J* = 6.3, Me_2CH); 9.41 (*s*, H–N(2)). ^{13}C-NMR ((D_6)DMSO): 13.7; 16.4; 18.2; 19.4; 19.9; 20.8; 31.7; 35.9; 47.5, 56.9, 61.6, 69.6, 172.7. ESI-MS: 252 ($[M+H]^+$). HR-ESI-MS: 242.2227 ($[M+H]^+$, $C_{13}H_{28}N_3O^+$; calc. 242.2227).

11.3. *(4*RS*,5*RS*)-1,5-Di(propan-2-yl)-4-(propan-2-ylamino)pyrazolidin-3-one* (**16c**). Prepared from **10d** (319 mg, 1 mmol) and **6d** (10 ml); 5 h. Yield: 227 mg (100%). Yellow oil. IR (NaCl): 3174, 3062, 2965, 2873, 1689, 1469, 1384, 1366, 1321, 1167, 1022, 944, 856. ^{1}H-NMR ((D_6)DMSO): 0.87 (*d*, *J* = 6.7, Me_2CH); 0.96, 0.98, 0.99, 1.00 (4*d*, 1:1:1:1, *J* = 6.4, 2 Me_2CH); 1.55 (br. *s*, NH); 1.58 (*sept.*, *J* = 6.4, Me_2CH); 2.78 (*dd*, *J* = 2.1, 5.8, H–C(5)); 2.92 (*d*, *J* = 2.1, H–C(4)); 2.93–3.00 (*m*, 2 Me_2CH); 9.40 (*s*, HN–C(4)). ^{13}C-NMR ((D_6)DMSO): 18.1; 18.4; 19.4; 20.8; 22.9; 22.9; 31.8; 46.3; 56.8; 58.8; 70.3; 137.2. ESI-MS: 228 ($[M+H]^+$). HR-ESI-MS: 228.2069 ($[M+H]^+$, $C_{12}H_{26}N_3O^+$; calc. 228.207).

11.4. *(4*RS*,5*RS*)-4-(Cyclohexylamino)-1,5-di(propan-2-yl)pyrazolidin-3-one* (**16d**). Prepared from **10d** (319 mg, 1 mmol) and **6e** (0.1036 ml, 1 mmol); 6 h. Yield: 286 mg (100%). Yellow oil. IR (NaCl): 3168, 3066, 2928, 2688, 1450, 1385, 1369, 1324, 1126, 1016, 948, 890, 846, 802. ^{1}H-NMR ((D_6)DMSO): 0.87, 0.96, 0.98 (3*d*, 2:1:1, *J* = 6.6, 2 Me_2CH); 0.94–1.00 (*m*, 1 H, C_6H_{11}); 1.08–1.25 (*m*, 3 H, C_6H_{11}); 1.51–1.61 (*m*, 3 H, C_6H_{11}, Me_2CH); 1.62–1.69 (*m*, 2 H, C_6H_{11}); 1.82–1.90 (*m*, 2 H, C_6H_{11}); 2.56–2.65 (*m*, 1 H, C_6H_{11}); 2.78 (*dd*, *J* = 2.3, 5.9, H–C(5)); 2.96 (*sept.*, *J* = 6.3, Me_2CH); 2.98–3.01 (*m*, H–C(4)); 3.34 (*s*, NH); 9.39 (*s*, H–N(2)). ^{13}C-NMR ((D_6)DMSO): 18.2; 18.4; 19.3; 20.8; 24.6; 24.7; 25.8; 31.8; 33.2; 33.3; 54.1; 56.9; 58.3; 70.4; 173.2. ESI-MS: 287 ($[M+H]^+$). HR-ESI-MS: 267.2311 ($[M+H]^+$, $C_{15}H_{30}N_3O^+$; calc. 268.2383).

11.5. *(4*RS*,5*RS*)-1,5-Di(propan-2-yl)-4-(propylamino)pyrazolidin-3-one* (**16e**). Prepared from **10d** (319 mg, 1 mmol) and **6n** (89 µl, 1.2 mmol); 5 h. Yield: 218 mg (96%). Dark-red oil. IR (NaCl): 3186, 2961, 2873, 1688, 1464, 1385, 1325, 1129, 948, 880, 794. ^{1}H-NMR ((D_6)DMSO): 0.82–0.89 (*m*, $MeCH_2$, Me_2CH); 0.96, 0.98 (2*d*, 1:1, *J* = 6.4, Me_2CH); 1.36–1.46 (*m*, CH_2); 1.56 (*sept.*, Me_2CH); 1.78 (br. *s*, HN–C(4)); 2.47–2.56, 2.57–2.66 (2*m*, 1:1, CH_2); 2.79 (*dd*, *J* = 2.2, 5.9, H–C(5)); 2.82 (br. *s*, H–C(4)); 2.96 (*sept.*, *J* = 6.4, Me_2CH); 9.41 (*s*, H–N(2)). ^{13}C-NMR ((D_6)DMSO): 18.1; 18.2; 19.3; 20.8; 31.6; 31.8; 35.9; 47.4; 56.8; 61.6; 69.6; 172.7. ESI-MS: 228 ($[M+H]^+$). HR-ESI-MS: 228.207 ($[M+H]^+$, $C_{12}H_{26}N_3O^+$; calc. 228.207).

11.6. *(4*RS*,5*RS*)-4-(Pentan-2-ylamino)-1,5-di(propan-2-yl)pyrazolidin-3-one* (**16f**). Prepared from **10d** (319 mg, 1 mmol) and **6o** (5 ml, excess); 13 h. Yield: 192 mg (75%), 2:1 mixture of diastereoisomers. Red oil. IR (NaCl): 3177, 3066, 2960, 2931, 2872, 1690, 1467, 1384, 1370, 1326, 1155, 1069, 1006, 946, 767, 692. ^{1}H-NMR ($CDCl_3$): major isomer: 0.84–0.92 (*m*, Me_2CH, $MeCH_2$); 1.01–1.06 (*m*, Me_2CH, 3 H of pentyl); 1.20–1.43 (*m*, 2 CH_2); 1.59–1.71 (*m*, Me_2CH); 2.70 (*sext.*, *J* = 6.2, 1 H, CH_2); 2.80 (*dd*, *J* = 2.0, 6.0, H–C(5)); 2.97 (br. *tq*, *J* = 3.4, 6.3, 1 H, CH_2); 3.05 (*sept.*, *J* = 6.4, Me_2CH); 3.17 (br. *d*, *J* = 1.8, H–C(4)); 9.09 (br. *s*, H–N(2)); minor isomer: 0.84–0.92 (*m*, Me_2CH, $MeCH_2$); 1.01–1.06 (*m*, Me_2CH, 3 H of pentyl); 1.20–1.43 (*m*, 2 CH_2); 1.59–1.71 (*m*, Me_2CH); 2.70 (*sext.*, *J* = 6.2, Me_2CH); 2.80 (*dd*, *J* = 2.0, 6.0, H–C(5)); 2.97 (br. *tq*, *J* = 3.4, 6.3, 1 H, CH_2); 3.05 (*sept.*, *J* = 6.4, Me_2CH); 3.13 (br. *d*, *J* = 2.2, H–C(4)); 9.09 (br. *s*, H–N(2)). ^{13}C-NMR ($CDCl_3$): major isomer: 14.3; 18.4; 18.8; 19.3; 19.4; 20.4; 20.9; 32.2; 40.0; 50.8; 57.9; 59.6; 71.1; 174.7; minor isomer: 14.3; 18.2; 18.7; 19.2; 19.2; 20.7; 20.9; 32.4; 39.5; 50.3; 57.8; 59.3; 71.6; 174.6. ESI-MS: 256 ($[M+H]^+$). HR-ESI-MS: 256.238 ($[M+H]^+$, $C_{14}H_{30}N_3O^+$; calc. 256.2383).

11.7. *(4*RS*,5*RS*)-4-(Cyclopentylamino)-1,5-di(propan-2-yl)pyrazolidin-3-one* (**16g**). Prepared from **10d** (319 mg, 1 mmol) and **6p** (89 µl, 1 mmol); 12 h. Yield: 234 mg (99%). Dark oil. IR (NaCl): 3180, 3066, 2958, 2871, 1689, 1571, 1466, 1385, 1368, 1324, 1203, 1169, 1012, 958, 888, 830, 799. ^{1}H-NMR ((D$_6$)DMSO): 0.86, 0.87 (2*d*, 1:1, *J* = 6.7, *Me*$_2$CH); 0.96, 0.98 (2*d*, 1:1, *J* = 6.3, *Me*$_2$CH); 1.24–1.33, 1.40–1.50 (2*m*, 1:1, CH$_2$); 1.53–1.63 (*m*, CH$_2$, Me$_2$C*H*); 1.69–1.81 (*m*, CH$_2$, C$_5$H$_9$); 2.04–2.10 (*m*, NH); 2.81 (*dd*, *J* = 5.9, 2.2, H–C(5)); 2.86 (*d*, *J* = 2.2, H–C(4)); 2.95 (*sept.*, *J* = 6.3, Me$_2$C*H*); 3.27 (*quint.*, *J* = 6.5, 1 H, C$_5$H$_9$); 9.40 (*s*, H–N(2)). ^{13}C-NMR ((D$_6$)DMSO): 18.2; 18.4; 19.8; 20.8; 22.7; 31.8; 32.6; 32.7; 37.8; 56.8; 57.7; 60.1; 70.0; 173.0. ESI-MS: 254 ([*M* + H]$^+$). HR-ESI-MS: 254.223 ([*M* + H]$^+$, C$_{14}$H$_{28}$N$_3$O$^+$; calc. 254.2227).

11.8. *(4*RS*,5*RS*)-4-(Cycloheptylamino)-1,5-di(propan-2-yl)pyrazolidin-3-one* (**16h**). Prepared from **10d** (319 mg, 1 mmol) and **6q** (0.168 ml, 1.4 mmol); 13 h. Yield: 281 mg (100%). Yellow oil. IR (NaCl): 3171, 3062, 2965, 2926, 2855, 1688, 1463, 1385, 1368, 1324, 1125, 1016, 950, 825, 772, 688. ^{1}H-NMR ((D$_6$)DMSO): 0.86, 0.87 (2*d*, 1:1, *J* = 6.7, Me$_2$C*H*); 0.96, 0.98 (2*d*, 1:1, *J* = 6.3, *Me*$_2$CH); 1.26–1.39 (*m*, 4 H, C$_7$H$_{14}$); 1.42–1.65 (*m*, 4 CH$_2$, C$_7$H$_{14}$, Me$_2$C*H*); 1.75–1.85 (*m*, NH); 2.77 (*dd*, *J* = 2.3, 6.0, H–C(5)); 2.80–2.86 (*m*, 1 H, C$_7$H$_{14}$); 2.92 (*d*, *J* = 2.3, H–C(4)); 2.96 (*sept.*, *J* = 6.3, Me$_2$C*H*); 9.39 (*s*, H–N(2)). ^{13}C-NMR (CDCl$_3$): 18.3; 18.6; 19.2; 20.9; 24.1; 24.2; 28.2; 28.4; 32.3; 34.7; 35.3; 56.9; 57.8; 59.2; 71.5; 174.5. ESI-MS: 282 ([*M* + H]$^+$). HR-ESI-MS: 282.2541 ([*M* + H]$^+$, C$_{16}$H$_{32}$N$_3$O$^+$; calc. 282.254).

11.9. *(4*RS*,5*RS*)-1,5-Di(propan-2-yl)-4-[(tetrahydrofuran-3-ylmethyl)amino]pyrazolidin-3-one* (**16i**). Prepared from **10d** (319 mg, 1 mmol) and **6r** (50% aq. soln., 0.227 ml, 1.3 mmol); 4 h. Yield: 269 mg (100%); 1:1 mixture of diastereoisomers. Yellow oil. IR (NaCl): 3232, 2966, 2872, 1686, 1468, 1386, 1369, 1325, 1204, 1156, 1130, 1076, 912, 801, 762. ^{1}H-NMR (CDCl$_3$): diastereoisomer 1: 0.93, 0.95 (2*d*, 1:1, *J* = 6.8, *Me*$_2$CH); 1.06–1.10 (*m*, *Me*$_2$CH); 1.53–1.66 (*m*, 1 H, CH$_2$); 1.70 (*sept.*, *J* = 6.7, Me$_2$C*H*); 2.00–2.08 (*m*, 1 H, CH$_2$); 2.29–2.45 (*m*, 2 H, NH, CH$_2$); 2.58 (*dd*, *J* = 8.6, 11.0, 1 H, CH$_2$); 2.77–2.85 (*m*, 1 H, CH$_2$); 2.83 (*dd*, *J* = 2.6, 6.1, H–C(5)); 3.02 (*sept.*, *J* = 6.4, Me$_2$C*H*); 3.09 (br. *d*, *J* = 2.6, H–C(4)); 3.50 (*dd*, *J* = 5.9, 8.7, 1 H, CH$_2$); 3.70–3.90 (*m*, 3 H, CH$_2$); H–N(2) exchanged; diastereoisomer 2: 0.93, 0.95 (2*d*, 1:1, *J* = 6.8, *Me*$_2$CH); 1.06–1.10 (*m*, *Me*$_2$CH); 1.53–1.66 (*m*, 1 H, CH$_2$); 1.70 (*sept.*, *J* = 6.7, Me$_2$C*H*); 2.00–2.08 (*m*, 1 H, CH$_2$); 2.29–2.45 (*m*, 2 H, NH, CH$_2$); 2.65 (*dd*, *J* = 7.6, 11.2, 1 H, CH$_2$); 2.77–2.85 (*m*, 1 H, CH$_2$); 2.83 (*dd*, *J* = 2.6, 6.1, H–C(5)); 3.02 (*sept.*, *J* = 6.4, Me$_2$C*H*); 3.12 (br. *d*, *J* = 2.6, H–C(4)); 3.54 (*dd*, *J* = 5.9, 8.7, 1 H, CH$_2$); 3.70–3.90 (*m*, 3 H, CH$_2$); H–N(2) exchanged. ^{13}C-NMR (CDCl$_3$): diastereoisomer 1: 18.3; 18.5; 18.9; 21.0; 30.5; 32.3; 39.8; 51.3; 57.7; 62.1; 67.8; 70.6; 71.8; 173.6; diastereoisomer 2: 18.4; 18.5; 18.9; 21.0; 30.6; 32.3; 39.8; 52.0; 57.8; 62.4; 67.9; 70.7; 72.2; 173.7. ESI-MS: 270 ([*M* + H]$^+$). HR-ESI-MS: 270.2176 ([*M* + H]$^+$, C$_{14}$H$_{28}$N$_3$O$_2^+$; calc. 270.2176).

12. *Synthesis of* N-*[(4*RS*,5*RS*)-3-Oxo-5-(propan-2-yl)pyrazolidin-4-yl]-1,1′-biphenyl-4-carboxamide* (**17**). A mixture of **20a** (153 mg, 0.77 mmol), DMF (5 ml), Et$_3$N (0.107 ml, 0.77 ml), and BPC (303 mg, 0.77 mmol) was stirred under Ar at r.t. for 2 h. Then, Et$_3$N (0.107 ml, 0.77 ml) and amine **13** (110 mg, 0.77 mmol) were added, and the mixture was stirred at r.t. for 12 h. Volatile components were evaporated *in vacuo*, and the residue was purified by FC (first AcOEt to elute the less-polar impurities, then AcOEt/MeOH 20:1, to elute the product). Fractions containing the product were combined and evaporated *in vacuo*. The residue was triturated with CH$_2$Cl$_2$ (5 ml), and the precipitate was collected by filtration to give **17**. Yield: 26 mg (10%). White solid. M.p. 221–223°. IR (KBr): 3266, 3067, 2955, 2922, 2867, 1724, 1640, 1607, 1561, 1536, 1499, 1482, 1448, 1426, 1403, 1388, 1364, 1313, 1294, 1277, 1258, 1194, 1179, 1108, 1077, 1006, 977, 912, 852, 819, 808, 767, 744, 728, 693. ^{1}H-NMR ((D$_6$)DMSO): 0.89, 0.92 (2*d*, 1:1, *J* = 6.6, *Me*$_2$CH); 1.78–1.90 (*m*, Me$_2$C*H*); 3.16 (*dd*, *J* = 8.8, 10.4, H–C(5)); 4.62 (*dd*, *J* = 9.2, 10.7, H–C(4)); 5.05 (br. *s*, H–N(1)); 7.40–8.06 (*m*, 9 arom. H); 8.76 (*d*, *J* = 9.0, NH); 9.34 (*s*, H–N(2)). ^{13}C-NMR ((D$_6$)DMSO): 18.7; 19.8; 21.2; 24.7; 30.3; 126.6; 126.9; 127.9; 128.3; 129.0; 130.0; 132.9; 139.1; 165.7; 167.2. ESI-MS: 324 ([*M* + H]$^+$). HR-ESI-MS: 324.1706 ([*M* + H]$^+$, C$_{19}$H$_{22}$N$_3$O$_2^+$; calc. 324.1707).

13. *General Procedure for the Synthesis of 4-[(Phenylacetyl)amino]pyrazolidin-3-ones* **18** *and* **19** (*GP 8*). A mixture **14a** or **15a** (1 mmol), anh. CH$_2$Cl$_2$ (5 ml), **20b** (141 mg, 1.04 mmol), and EEDQ (270 mg, 1.09 mmol) was stirred under Ar for 24 h. Volatile components were evaporated *in vacuo*, and the residue was purified by CC (AcOEt/hexanes 1:1). Fractions containing the product were combined and evaporated *in vacuo* to give **18** or **19**.

13.1. N-*[(4*RS*,5*RS*)-3-Oxo-1,5-di(propan-2-yl)pyrazolidin-4-yl]-2-phenylacetamide* (**18**). Prepared from **14a** (168 mg, 0.91 mmol). Yield: 229 mg (83%). White solid. M.p. 155–160°. IR (KBr): 3374, 3239,

3187, 3061, 2970, 2871, 1714, 1691, 1660, 1639, 1603, 1556, 1495, 1468, 1455, 1442, 1384, 1366, 1333, 1311, 1283, 1162, 1148, 1071, 1013, 883, 770, 733, 695. ^{1}H-NMR ((D$_6$)DMSO): 0.81, 0.88 (2*d*, 1:1, *J* = 6.8, *Me*$_2$CH); 0.98, 0.99 (2*d*, 1:1, *J* = 6.1, *Me*$_2$CH); 1.76 (*dsept.*, *J* = 1.5, 6.6, Me$_2$C*H*); 2.73 (*t*, *J* = 5.1, H–C(5)); 2.89 (*sept.*, *J* = 6.3, Me$_2$C*H*); 3.44, 3.48 (2*d*, 1:1, *J* = 13.8, CH$_2$); 4.09 (*dd*, *J* = 5.1, 7.8, H–C(4)); 7.20–7.33 (*m*, 5 arom. H); 8.69 (*d*, *J* = 7.9, NH); 9.68 (*s*, H–N(2)). ^{13}C-NMR ((D$_6$)DMSO): 17.7; 18.0; 18.0; 20.8; 30.9; 42.0; 52.2; 55.8; 69.8; 126.3; 128.2; 128.9; 136.2; 169.4; 169.7. ESI-MS: 304 ([*M* + H]$^+$). HR-ESI-MS: 304.2017 ([*M* + H]$^+$, $C_{17}H_{26}N_3O_2^+$; calc. 304.2020). Anal. calc. for $C_{17}H_{25}N_3O_2 \cdot 1/8\ H_2O$ (305.65): C 66.80, H 8.33, N 13.75; found: C 66.61, H 8.45, N 13.85.

13.2. N-*[(4*RS,*5*RS*)-1-Benzyl-2-methyl-3-oxo-5-(propan-2-yl)pyrazolidin-4-yl]-2-phenylacetamide* (**19**). Prepared from **15a** (257 mg, 1.04 mmol). Yield: 288 mg (82%). Yellow solid. M.p. 141–145°. IR (KBr): 3260, 3206, 3060, 3031, 2960, 2928, 2870, 1660, 1603, 1585, 1543, 1494, 1464, 1454, 1429, 1405, 1386, 1368, 1355, 1343, 1332, 1311, 1296, 1282, 1215, 1160, 1127, 1099, 1064, 1030, 1005, 982, 930, 918, 899, 845, 808, 753, 731, 718, 698, 671, 623, 611. ^{1}H-NMR ($CDCl_3$): 0.80, 0.82 (2*d*, 1:1, *J* = 6.8, *Me*$_2$CH); 1.76 (*dsept.*, *J* = 1.6, 6.8, Me$_2$C*H*); 2.85 (*dd*, *J* = 2.5, 5.1, H–C(5)); 3.03 (*s*, Me); 3.35, 3.39 (2*d*, 1:1, *J* = 19.0, CH$_2$); 3.81, 3.86 (2*d*, 1:1, *J* = 13.6, CH$_2$); 4.18 (*dd*, *J* = 2.4, 7.1, H–C(4)); 5.11 (*d*, *J* = 7.0, NH); 7.10–7.14, 7.21–7.38 (2*m*, 1:4, 10 arom. H). ^{13}C-NMR ($CDCl_3$): 17.3; 18.9; 30.5; 32.1; 43.4; 54.7; 60.5; 69.8; 127.4; 128.4; 128.8; 129.0; 129.4; 130.4; 134.8; 135.4; 168.8; 170.7. ESI-MS: 366 ([*M* + H]$^+$). HR-ESI-MS: 366.2175 ([*M* + H]$^+$, $C_{22}H_{28}N_3O_2^+$; calc. 366.2176). Anal. calc. for $C_{22}H_{27}N_3O_2 \cdot 1/6\ H_2O$ (368.47): C 72.30, H 7.45, N 11.50; found: C 71.96, H 7.47, N 11.49.

12. *X-Ray Crystal-Structure Analysis of Compounds* **9k**, **10f**, *and* **12e** (*Figs. 3–5* and *Table 4*)[3]). For X-ray crystal-structure determination, the crystals of the compounds **9k**, **10f**, and **12e** were mounted on the tip of glass fibres and transferred to the goniometer head. Diffraction data for **10f** were collected on a *Nonius Kappa CCD* diffractometer using monochromated MoK_α radiation at 150 K by using Nonius Collect software [32]. Data reduction and integration were performed with the software package DENZO-SMN [33]. Diffraction data for **9k** and **12e** were collected on *SuperNova* X-ray single-crystal diffractometer equipped with *Atlas* detector using monochromated MoK_α radiation at r.t.; in this case, the data reduction and integration were performed with the software package CrysAlis PRO [34]. The coordinates of all of the non-H-atoms were found *via* direct methods using the SIR97 or Superflip structure solution programs [35][36]. A full-matrix least-squares refinement on F^2 magnitudes with anisotropic displacement parameters for all non-H-atoms using SHELXL-97 was employed [37]. All H-atoms were initially located in difference *Fourier* maps. All H-atoms attached to C-atom were subsequently treated as riding atoms in geometrically idealized positions with C–H bond lengths of 0.96 Å for Me, 0.97 Å for CH$_2$, 0.98 Å for CH, and 0.93 Å for aromatic C–H bonds. The corresponding displacement parameters U_{iso}(H) were 1.5-times higher than those of the carrier Me C-atoms and 1.2-times higher than all other H-bearing C-atoms. H-Atoms attached to N-atoms and (possibly) taking part in H-bonding were found in the difference electron-density maps and refined isotropically with the constraint *U*iso(H) = 1.2 U_{iso}(N). When the obtained N–H distances were too long, the appropriate bond length restraints were used (N–H with lengths of 0.87(2) Å). Crystal data, data collection, and structure refinement for compounds **9k**, **10f**, and **12e** are compiled in *Table 4*. Figures depicting the structures were drawn by ORTEP3 [38].

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[3]) CCDC-930454–930456 contain the supplementary crystallographic data for **9k**, **10f**, and **12e**, resp. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

Table 4. *Crystallographic Data for Compounds* **9k**, **10f**, *and* **18**

	9k	**10f**	**18**
Empirical formula	$C_{20}H_{20}N_4O_5$	$C_{20}H_{23}N_3O_3$	$C_{22}H_{27}N_3O_2$
M_r	396.40	353.41	365.47
Crystal habit, color	prism, colorless	platelet, colorless	prism, colorless
Crystal system	monoclinic	monoclinic	monoclinic
Crystal dimensions [mm]	$0.30 \times 0.15 \times 0.10$	$0.50 \times 0.25 \times 0.02$	$0.30 \times 0.15 \times 0.10$
Temp. [K]	150(2)	150(2)	293(2)
Space group	$P12_1/n$ 1	$P12_1/c$ 1	$C12/c$ 1
Z	4	4	8
Unit cell parameters:			
a [Å]	15.5657(5)	11.3943(2)	28.3750(7)
b [Å]	8.2240(2)	18.5977(4)	8.8964(2)
c [Å]	15.9538(5)	9.6578(2)	16.2347(4)
β [°]	110.316(4)	112.2710(10)	90.413(2)
V [Å^3]	1915.24(10)	1893.89(7)	4098.11(17)
D_x (Mg m^{-3})	1.375	1.239	1.185
Radiation type	MoK_α	MoK_α	MoK_α
μ [mm^{-1}]	0.101	0.085	0.077
Diffractometer	*SuperNova*, Dual, Cu at zero, Atlas	*Nonius Kappa CCD*	*SuperNova*, Dual, Cu at zero, Atlas
Scan type	ω	ω	ω
Absorption correction	multi-scan	multi-scan	multi-scan
Total reflections measured	11172	34551	19555
Independent reflections	4394	4349	4705
Observed reflections	3331	3215	3419
Criterion for obs. reflections	$F^2 > 2.0\ \sigma(F^2)$	$F^2 > 2.0\ \sigma(F^2)$	$F^2 > 2.0\ \sigma(F^2)$
Rint	0.0281	0.045	0.0283
θ Range [°]	2.83 – 27.48	1.93 – 27.51	2.87 – 27.48
h Range	− 20 – 12	− 14 – 14	− 36 – 36
k Range	− 10 – 10	− 24 – 24	− 11 – 11
l Range	− 20 – 20	− 12 – 12	− 21 – 21
Refinement on	F^2	F^2	F^2
R (on F_{obs}), wR (on F_{obs}), S	0.0457, 0.1118, 1.030	0.0579, 0.1451, 1.150	0.0574, 0.1552, 1.039
Total contributing reflections	4394	4349	4705
No. of parameters	268	246	251
H-Atom treatment	C-bonded treated as riding, N-bonded refined isotropically	C-bonded treated as riding, N-bonded refined isotropically	C-bonded treated as riding, N-bonded refined isotropically
$(\Delta/\sigma)_{max}$; $(\Delta/\sigma)_{ave}$	< 0.001; < 0.001	< 0.001; < 0.001	< 0.001; < 0.001
ρ_{max}; ρ_{min} [eÅ^{-3}]	0.251; − 0.209	0.530; − 0.499	0.319; − 0.242

REFERENCES

[1] H. Dorn, *Chem. Heterocycl. Compd. USSR* **1981**, 3.
[2] R. M. Claramunt, J. Elguero, *Org. Proc. Prep. Int.* **1991**, *23*, 273.
[3] L. Yet, 'Pyrazoles', in 'Comprehensive Heterocyclic Chemistry III', Eds. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, Vol. 4, Ed. J. Joule, Elsevier Science, Oxford, 2008, p. 1; and refs. cit. therein; J. Elguero, 'Pyrazoles', in 'Comprehensive Heterocyclic Chemistry II', Eds.

A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Vol. 3, Ed. I. Shinkai, Elsevier Science, Oxford, 1996, p. 1; and refs. cit. therein; B. Stanovnik, J. Svete, in 'Pyrazoles', in 'Science of Synthesis, Houben-Weyl Methods of Organic Transformations', Vol. 12, Ed. R. Neier, Georg Thieme, Stuttgart, 2002, p. 15, and refs. cit. therein.

[4] J. Svete, '(4*R**,5*R**)-4-Benzoylamino-5-phenylpyrazolidin-3-one – A Useful Building Block in the Synthesis of Functionalized Pyrazoles', in 'Stereochemistry Research Trends', Eds. M. A. Horvat, J. H. Golob, Nova Science Publishers, New York, 2008, p. 129; and refs. cit. therein.

[5] K. Meier, *Bild Ton* **1970**, *23*, 85.

[6] B. J. Whittle, *Acta Obstet. Gyn. Scand., Suppl.* **1979**, *87*, 21.

[7] R. J. Ternansky, S. E. Draheim, *Tetrahedron* **1992**, *48*, 777; and refs. cit. therein.

[8] M. P. Sibi, L. M. Stanley, X. Nie, L. Venkatraman, M. Liu, C. P. Jasperse, *J. Am. Chem. Soc.* **2007**, *129*, 395.

[9] H. Nakano, N. Tsugawa, K. Takahashi, Y. Okuyama, R. Fujita, *Tetrahedron* **2006**, *62*, 10879.

[10] M. P. Sibi, T. Soeta, *J. Am. Chem. Soc.* **2007**, *129*, 4522.

[11] C.-H. Lin, K.-S. Yang, J.-F. Pan, K. Chen, *Tetrahedron Lett.* **2000**, *41*, 6815.

[12] R. Shintani, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 10778.

[13] L. Pezdirc, B. Stanovnik, J. Svete, *Aust. J. Chem.* **2009**, *62*, 1661.

[14] M. Keller, A. S. S. Sido, P. Pale, J. Sommer, *Chem. – Eur. J.* **2009**, *15*, 2810.

[15] S. R. Snavely, G. R. Hodges, *Ann. Intern. Med.* **1984**, *101*, 92.

[16] M. R. Holdiness, *Med. Toxicol.* **1987**, *2*, 33.

[17] S. G. Hofmann, A. T. Sawyer, A. Asnaani, *Curr. Pharm. Design* **2012**, *18*, 5659.

[18] C. R. Pawlak, F.-S. Chen, F.-Y. Wu, Y.-J. Ho, *Kaohsiung J. Med. Sci.* **2012**, *28*, 407.

[19] S. Zupančič, J. Svete, B. Stanovnik, *J. Heterocycl. Chem.* **1999**, *36*, 607.

[20] A. Novak, J. Bezenšek, U. Grošelj, A. Golobič, B. Stanovnik, J. Svete, *Arkivoc* **2011**, (*vi*), 18.

[21] N. Tamura, Y. Matsushita, K. Yoshioka, M. Ochiai, *Tetrahedron* **1988**, *44*, 3231.

[22] L. N. Jungheim, S. K. Sigmund, *J. Org. Chem.* **1987**, 52, 4007.

[23] U. Schmidt, H. Griesser, V. Lietenberger, A. Lieberknecht, R. Mangold, R. Meyer, B. Riedl, *Synthesis* **1992**, 487.

[24] A. Novak, A. Testen, J. Bezenšek, U. Grošelj, M. Hrast, M. Kasunič, S. Gobec, B. Stanovnik, J. Svete, *Tetrahedron* **2013**, *69*, 6648.

[25] H. Barreteau, A. Kovač, A. Boniface, M. Sova, S. Gobec, D. Blanot, *FEMS Microbiol. Rev.* **2008**, *32*, 168.

[26] P. A. Lanzetta, L. J. Alvarez, P. S. Reinach, O. A. Candia, *Anal. Biochem.* **1979**, *100*, 95.

[27] I. Photaki, *J. Am. Chem. Soc.* **1963**, *85*, 1123.

[28] U. Schmidt, A. Lieberknecht, J. Wild, *Synthesis* **1984**, 53.

[29] a) F. Effenberger, J. Kühlwein, C. Baumgartner, *Liebigs Ann. Chem.* **1994**, 1069; b) F. Effenberger, J. Kühlwein, K. Drauz, *Liebigs Ann. Chem.* **1993**, 1295; c) T. A. Stammers, M. J. Burk, *Tetrahedron Lett.* **1999**, *40*, 3325.

[30] H. W. Krause, H.-J. Kreuzfeld, U. Schmidt, C. Dobler, M. Michalik, S. Taudien, C. Fischer, *Chirality* **1996**, *8*, 173.

[31] C. Becker, B. Dembofsky, R. Jacobs, J. Kang, C. Ohnmacht, J. Rosamond, A. B. Shenvi, T. Simpson, J. Woods, WO 2004031154; CAN140:339634; K. Hudson, N. Laing, P. Lewis, WO 2007104933; CAN147:386252.

[32] Collect Software, Nonius, BV, Delft, The Netherlands, 2000.

[33] Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307.

[34] CrysAlis PRO, Oxford Diffraction Ltd., Yarnton, Oxfordshire, England, 2011.

[35] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115.

[36] L. Palatinus, G. Chapuis, *J. Appl. Crystallogr.* **2007**, *40*, 786.

[37] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **2008**, *64*, 112.

[38] L. J. Farrugia, *J. Appl. Crystallogr.* **1997**, *30*, 565.

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