Synthesis and Transformations of Novel L-Phenylalanine Derived Pyrazolidin-3-ones

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ABSTRACT A simple and straightforward four-step synthesis of novel diastereomeric L-phenylalanine-derived pyrazolidin-3-ones is described. The absolute configuration of the novel C(5) stereogenic centre has been unambiguously determined by single crystal X-ray analysis and *via* chemical interconversions. A series of novel thiourea derived pyrazolidinones have been prepared and tested as potential organocatalysts. N(1) un-substituted pyrazolidinones can be used for the construction of a novel type of bicyclic heterocycles and other selective derivatizations. *Chirality 25:541–555, 2013.*

KEY WORDS: β-keto ester; hydrazine cyclization; pyrazolidin-3-ones; (thio)ureas; tetrahydro-1*H*-imidazo[1,5-*b*]pyrazole-2,6-dione

INTRODUCTION

Pyrazolidin-3-one derivatives, both mono and bicyclic, remain attractive targets due to their diverse applicabilities and bioactivities as well as the challenges associated with their enantio- and/or diastereoselective synthesis. Thus, pyrazolidinone derivatives have been employed as dyes in food and other industries.[1–3] Their bioactivities range from analgesic and antipyretic in phenazone,[4–6] anti-inflammatory in phenylbutazone,[4–6] anorectic in BW357U,[7] to inhibitory activities of cyclooxygenase and lipoxygenase in BW755C and phenidone, respectively.[8,9] Bicyclic pyrazolidinones are used, among others, as drugs to relieve Alzheimer's disease[10] and as antibacterial agents.[11–15] Camphor derived pyrazolidin-3-one has been successfully employed as chiral auxiliary[16–21] while achiral pyrazolidinone templates have been used in enantioselective *Diels-Alder* cycloadditions in conjunction with chiral Lewis acids.[22–24] Several studies have demonstrated the potential of pyrazolidin-3-ones as a new scaffold in organocatalysis. Ogilvie and co-workers successfully applied camphor derived pyrazolidin-3-one as a covalent organocatalyst in cycloaddition reactions,[25–28] while Smith *et al.* studied structural effects in pyrazolidin-3-one mediated organocatalytic Diels-Alder reactions.[29] Research into acyclic- and cyclic 5- and 6-membered hidrazides conducted by Tomkinson *et al.* may come useful in the design of novel pyrazolidin-3-one catalysts and their 6-membered counterparts.[30–32]

For further development of pyrazolidin-3-one derivatives in asymmetric catalysis, and other applications, an easy access to nonracemic pyrazolidin-3-one templates with diverse substituents at C(4)- and/or C(5)-positions, with the desired spatial orientation, are needed. Nonracemic pyrazolidin-3-ones have been accessed *via* simple diastereoizomeric derivatization of racemic pyrazolidinones followed by separation/deprotection.[29] Highly enantioselective addition of monosubstituted hydrazines to α,β-unsaturated imides using catalytic amounts of chiral Lewis acids has been reported giving N(1) and C(5)-substituted pyrazolidin-3-ones.[33] Asymmetric organocatalyzed synthesis of N(1), N(2) protected 5-alkyl substituted pirazolidin-3-ones based on the aza-Michael/hemiaminalization reaction of α,β-unsaturated aldehydes and hydrazides under iminium activation followed by PCC oxidation has been reported.[34] N(1)- and C(5)-Disubstituted pirazolidin-3-ones have been prepared using Diels-Alder cycloaddition strategy for the kinetic resolution of chiral pyrazolidinones.[35] Similarly, kinetic resolutions of azomethine imines via copper-catalyzed [3+2] cycloadditions gave pirazolidinones as single enantiomers.[36] Rhodium-catalyzed asymmetric arylation of azomethine imines yielded chiral 1-(diarylmethyl)pyrazolidin-3-ones.[37] Direct electrophilic amination of homoenolates catalyzed by *N*-heterocyclic carbenes furnished trisubstituted pyrazolidinones[38] while diastereoselective 1,3-dipolar cycloaddition of hydrazones with α-oxo-ketenes gave spiropyrazolidin-3-ones.[39] Highly enantioselective *Brønsted* acid catalyzed cycloaddition between alkenes and N-benzoylhydrazones lead to various optically active pyrazolidine derivatives.[40] Nonracemic pyrazolidinones have been prepared from enantiomerically pure 2,3-disubstituted oxirane carboxylic acids.[41] Ring switching methodology was used to prepare optically active diastereoizomeric pyrazolidin-3-ones.[42–44]

To the best of our knowledge, we could find no chiral nonracemic C(5)-substituted pyrazolidin-3-one diastereoisomers of type **A** prepared from chiral pool amino acid derivatives (Scheme 1). A literature search for compounds of type **A** revealed pyrazolidin-3-ones with alanine[43] and serine[42,44] side chain residue (R) and a non-proteinogenic side chain (R = CO_2R)[45]. This prompted us to investigate the preparation of pyrazolidin-3-ones of type **A** starting from N-Cbz-protected L-phenylalanine as a model amino acid *via* the corresponding keto ester, and cyclization with hydrazines in the final step. Additional functionalizations

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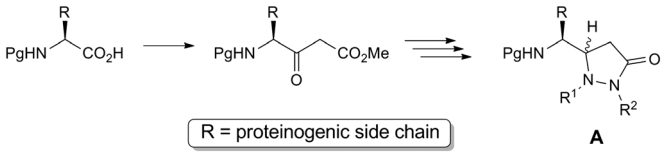


Scheme 1. Synthesis of α-amino acid derived pyrazolidin-3-ones.

of pyrazolidinones were carried out in order to establish the configuration of the newly created stereogenic centre as well as to prepare some potential new organocatalysts. The results of this preliminary study are reported herein.

EXPERIMENTAL

Materials and Methods

All reactions were performed under Argon in dried glassware using anhydrous solvents, except when using aqueous reagents. Solvents for extractions and chromatography were of technical grade and were distilled prior to use. Extracts were dried over technical grade Na_2SO_4. Melting points were determined on a Kofler micro hot stage and on SRS OptiMelt MPA100-Automated Melting Point System (Stanford Research Systems, Sunnyvale, CA, USA). The NMR spectra were obtained on a Bruker UltraShield 500 plus (Bruker, Billerica, MA, USA) at 500 MHz for ^{1}H and 126 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS (Agilent Technologies, Santa Clara, CA, USA), IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer (PerkinElmer, Waltham, MA, USA). Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II (PerkinElmer). Catalytic hydrogenation was performed on a Parr Pressure Reaction Hydrogenation Apparatus (Moline, IL, USA). Column chromatography (CC) was performed on silica gel (Silica gel 60, particle size: 0.035-0.070 mm, (Sigma-Aldrich, St. Louis, MO, USA). Medium-pressure liquid chromatography (MPLC) was performed with Büchi Flash Chromatography System (BUCHI Labortechnik AG, Flawil, Switzerland) (Büchi Fraction Collector C-660, Büchi Pump Module C-605, Büchi Control Unit C-620) on silica gel (LiChrosphere Si 60 (12 μm) and/or LiChroprep Si 60 (15-25 μm) (Merck, KGaA, Darmstadt, Germany); column dimensions (wet filled): 22 × 460 mm, 36 × 460 mm and 40 × 460 mm; backpressure: 10–20 Bar; detection: UV 254 nm. Low temperatures were maintained using Julabo FT902 immersion cooler (JULABO GmbH, Seelbach, Germany).

All chemicals were of reagent grade and used as supplied, unless stated otherwise. Z-L-phenylalanine (**1**), carbonyl-1,1'-diimidazole (CDI), lithium diisopropylamide (LDA), THF (anhydrous), MeOAc, $NaBH_4$, MsCl, hydrazine, methylhydrazine, *trans*-cinnamaldehyde, 1-methylindole, dimethyl malonate, *trans*-β-nitrostyrene, 10% palladium on charcoal, DMF (anhydrous), Boc_2O, MeI, *t*BuOK, HCHO, $NaCNBH_3$, trifluoroacetic acid (TFA), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**13**), 1-isothiocyanatonaphthalene (**19**), phenyl isocyanate (**21**), 4-methylphenyl isocyanate (**22**), and 4-bromophenyl isocyanate (**25**) were purchased from Sigma-Aldrich.

Source of chirality: Z-L-phenylalanine (**1**), product number 359807, $[\alpha]_D^{r.t.}$ = +5 (c = 5 in acetic acid), ee not specified, mp 85-87 °C.

Syntheses

The structures of novel compounds **3**, **4**, **5-7/5'-7'**, **8**, **9-12/9'-12'**, **14**, **15**, **16/16'**, **18/18'**, **20/20'**, **23**, **24**, and **26/26'** were determined by spectroscopic methods (^{1}H-NMR, ^{13}C-NMR, 2D-NMR, IR, HRMS) and by elemental analyses for C, H, and N. Compounds **4**, **5/5'**, **6/6'**, **8**, **9'**, **10/10'**, **12/12'**, **14**, **15**, **16/16'**, **20/20'**, and **24** were not obtained in analytically pure form. Their identities were confirmed by ^{13}C-NMR and HRMS. Mixtures of epimers **5/5'**, **11/11'**, and **12/12'** were characterized as mixtures of epimers. Single compounds or mixtures of epimers **8/8'**, **15/15'**, **17**, and **17'** were used in the following transformation without any or partial characterization.

Catalytic hydrogenation–General Procedure 1 (GP1). To a solution or suspension of amine(s) (1 equivalent) in MeOH (V) under argon was added Pd–C (10% on C), the reaction vessel was flushed with H_2, and the reaction mixture was hydrogenated in a *Paar* hydrogenator (P = 4 Bar) at room temperature for 1 h. The reaction mixture was filtered through a plug of Celite and washed with MeOH (100 mL). Volatile components were evaporated *in vacuo*, and the residue was dried on high vacuum and used in the following transformations without further purification.

Preparation of (thio)urea derivatives–General Procedure 2 (GP2). To a solution or suspension of amine(s) (1 equivalent) in anhydrous solvent (V) under argon at 0 °C was added iso (thio)cyanate (1 equivalent) and the resulting mixture was stirred for 30 minutes at 0 °C and 24 h at room temperature. Volatile components were evaporated *in vacuo* and the residue was purified/separated by column chromatography (CC) or MPLC. Fractions containing the separated product(s) were combined and volatile components evaporated *in vacuo*.

(*S*)-Methyl 4-(((benzyloxy)carbonyl)amino)-3-oxo-5-phenylpentanoate[46] (2). Carbonyl-1,1'-diimidazole (CDI) (7.89 g, 43.8 mmol) was added at room temperature to a stirred solution of (*S*)-2-(((benzyloxy)carbonyl)amino)-3-phenylpropanoic acid (**1**) (11.92 g, 39.8 mmol) in anhydrous THF (80 mL) under argon. The resulting mixture was stirred for 2 h at room temperature and used in the next step without any purification. Meanwhile, a solution of lithium enolate of MeOAc was prepared in the following way. LDA (90 mL, c = 2 M (in THF/heptane/ethylbenzene), 180 mmol) was added to anhydrous THF (80 mL) at –61 °C under argon, followed by dropwise addition of a solution of anhydrous MeOAc (14.3 mL, 180 mmol) in anhydrous THF (20 mL) under argon at –61 °C over a period of 15 minutes. After stirring of enolate at –61 °C for 1.5 h, the above prepared solution of imidazolide of **1** was added dropwise over the period of 30 minutes. The resulting mixture was stirred for 2 h and then quenched at –61 °C with $NaHSO_4$ (1 M in H_2O) and extracted with EtOAc (3 × 200 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat., 2 × 50 mL) and NaCl (aq. sat., 50 mL), dried over anhydrous Na_2SO_4, and volatile components evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc/petroleum ether = 1:4). Fractions containing the product **2** were combined and volatile components evaporated *in vacuo*. Yield: 6.08 g (43%) of yellowish solid; mp 79–80 °C (lit[46]: mp = 78-80 °C). $[\alpha]_D^{r.t.}$ = +8.8 (c = 0.16, $CHCl_3$). ($C_{20}H_{21}NO_5$ requires: C, 67.59; H, 5.96; N, 3.94; found C, 67.48; H, 5.80; N, 3.97); EI-HRMS: *m/z* = 356.1493 (MH^+); $C_{20}H_{22}NO_5$ requires: *m/z* = 356.1492 (MH^+); ν_{max} 3337, 3031, 2952, 1708, 1604, 1513, 1497, 1454, 1437, 1401, 1318, 1241, 1148, 1075, 1042, 1027, 844, 738, 697 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.70 (*dd*, *J* = 13.9; 10.6 Hz, Ha-C(5)); 3.10 (*dd*, *J* = 13.9; 4.3 Hz, Hb-C(5)); 3.62 (*s*, CO_2Me); 3.71 (*s*, $H_2C(2)$); 4.35 (*ddd*, *J* = 10.6; 8.2; 4.3 Hz, H-C(4)); 4.97 (*s*, CH_2); 7.19–7.37 (*m*, 10H of Ph); 7.81 (*d*, *J* = 8.3 Hz, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 34.7, 45.8, 51.9, 61.4, 65.5, 126.4, 127.5, 127.8, 128.2, 128.3, 129.2, 136.9, 137.7, 156.0, 167.4, 202.4.

(3*R*,4*S*)-Methyl 4-(((benzyloxy)carbonyl)amino)-3-hydroxy-5-phenylpentanoate (3) and (3*S*,4*S*)-methyl 4-(((benzyloxy)carbonyl)amino)-3-hydroxy-5-phenylpentanoate[47] (3'). To a solution of β-keto ester **2** (2.79 g, 7.85 mmol) in MeOH (30 mL)

cooled to –5 °C was added $NaBH_4$ (305 mg, 7.85 mmol) and the resulting mixture was stirred at –5 °C for 1 h and then quenched at –5 °C by the addition of H_2O (150 mL) followed by the addition of HCl (10 mL, 1 M in H_2O). The resulting suspension was stirred at 0 °C for 30 minutes, filtered, the collected product washed with H_2O (200 mL), and dried on high vacuum. Yield: 2.33 g (83%) of white solid (**3**:**3'** = 1:0.16). The epimers **3/3'** were separated by MPLC (EtOAC/petroleum ether = 1:2). Fractions containing the separated epimers **3/3'** were combined, respectively, and volatile components evaporated *in vacuo*. Alternatively, re-crystallization of the epimer mixture **3/3'** from EtOAc/*n*-heptane gave pure **3**.

Compound **3'**: Elutes first. Yield: 224 mg (8%) of white solid; mp 95-98 °C (lit[47]: mp = 99.5 °C). EI-HRMS: *m/z* = 358.1646 (MH^+); $C_{20}H_{24}NO_5$ requires: *m/z* = 358.1649 (MH^+). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.29 (*dd*, *J* = 15.4, 9.6 Hz, Ha-C(2)); 2.48 (*d*, *J* = 15.4; 3.4 Hz, Hb-C(2)); 2.58 (*dd*, *J* = 13.7; 10.1 Hz, Ha-C(5)); 2.86 (*dd*, *J* = 13.7; 4.5 Hz, Hb-C(5)); 3.58 (*s*, CO_2Me); 3.69–3.77 (*m*, H-C(4)); 3.93–4.00 (*m*, H-C(3)); 4.93 (*d*, *J* = 12.9 Hz, Ha of CH_2); 4.97 (*d*, *J* = 12.9 Hz, Hb of CH_2); 5.13 (*d*, *J* = 5.7 Hz, OH); 7.13 (*d*, *J* = 9.2 Hz, NH); 7.17–7.35 (*m*, 10H of Ph).

Compound **3**: Elutes second. Yield: 1.68 g (60%) of yellowish solid; mp 131-133 °C. $[\alpha]_D^{r.t.}$ = –4.3 (c = 0.07, $CHCl_3$). ($C_{20}H_{23}NO_5$ requires: C, 67.21; H, 6.49; N, 3.92. found C, 67.05; H, 6.25; N, 3.94); EI-HRMS: *m/z* = 358.1648 (MH^+); $C_{20}H_{24}NO_5$ requires: *m/z* = 358.1649 (MH^+); ν_{max} 3323, 3031, 2948, 1728, 1695, 1604, 1534, 1496, 1438, 1373, 1358, 1302, 1260, 1233, 1192, 1164, 1141, 1101, 1085, 1049, 1015, 981, 911, 883, 840, 775, 761, 738, 694, 609 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.37 (*dd*, *J* = 15.0; 9.5 Hz, Ha-C(2)); 2.55–2.64 (*m*, Hb-C (2), Ha-C(5)); 3.08 (*dd*, *J* = 13.9; 3.1 Hz, Hb-C(5)); 3.58–3.69 (*m*, CO_2Me, H-C(4)); 3.85–3.93 (*m*, H-C(3)); 4.92 (*d*, *J* = 12.9 Hz, Ha of CH_2); 5.00 (*d*, *J* = 12.9, Hb of CH_2); 5.27 (*d*, *J* = 6.8 Hz, OH); 7.18–7.41 (*m*, 10H of Ph, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 35.9, 39.4, 51.3, 57.3, 64.8, 70.3, 125.8, 127.2, 127.6, 128.0, 128.3, 129.1, 137.4, 139.4, 155.9, 172.0.

(3*R*,4*S*)-Methyl 4-(((benzyloxy)carbonyl)amino)-3-((methylsulfonyl)oxy)-5-phenylpentanoate (4). To a solution of β-hydroxy ester **3** (762 mg, 2.13 mmol) in pyridine (5 mL, 61.8 mmol) cooled to –5 °C was added MsCl (214 µL, 2.77 mmol) and the resulting mixture was stirred at –5 °C for 1 h and further 2 h at room temperature. The reaction mixture was poured into cooled (0 °C) PhMe (150 mL) and washed thoroughly with HCl (70 mL, 1 M in H_2O). The aqueous phase was discarded and the organic phase was washed with NaCl (aq. sat, 2 × 50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated *in vacuo* to give crude **4** used in the following transformations without further purifications. Yield: 653 mg (70%) of white solid; mp 117–125 °C. $[\alpha]_D^{r.t.}$ = –38.3 (c = 0.08, $CHCl_3$). ($C_{21}H_{25}NO_7S$ requires: C, 57.92; H, 5.79; N, 3.22; found C, 58.86; H, 5.77; N, 3.32); EI-HRMS: *m/z* = 436.1435 (MH^+); $C_{21}H_{26}NO_7S$ requires: *m/z* = 436.1424 (MH^+); ν_{max} 3294, 3057, 1739, 1681, 1544, 1495, 1455, 1439, 1399, 1384, 1346, 1320, 1271, 1246, 1223, 1206, 1172, 1141, 1088, 1038, 1027, 1001, 985, 968, 920, 892, 822, 799, 778, 752, 705, 671, 613 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.58 (*dd*, *J* = 13.8; 11.3 Hz, Ha-C(5)); 2.75 (*dd*, *J* = 16.1; 8.5 Hz, Ha-C (2)); 2.88–2.96 (*m*, Hb-C(2), Hb-C(5)); 3.17 (*s*, OSO_2Me); 3.63 (*s*, CO_2Me); 4.06–4.14 (*m*, H-C(4)); 4.91 (*d*, *J* = 12.8 Hz, Ha of CH_2); 4.97 (*d*, *J* = 12.8 Hz, Hb of CH_2); 5.03 (*dt*, *J* = 8.5; 4.2 Hz, H-C(3)); 7.14–7.35 (*m*, 10H of Ph); 7.52 (*d*, *J* = 9.1 Hz, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 34.9, 36.0, 38.1, 51.8, 55.0, 65.1, 79.7, 126.3, 127.3, 127.6, 128.2, 128.3, 129.0, 137.1, 138.0, 155.9, 170.0.

Benzyl ((*S*)-1-((*R*)-5-oxopyrazolidin-3-yl)-2-phenylethyl)carbamate (5) and benzyl ((*S*)-1-((*S*)-5-oxopyrazolidin-3-yl)-2-phenylethyl) carbamate (5'). To a solution of mesylate **4** (3.18 g, 7.3 mmol) in CH_2Cl_2 (50 mL) was added hydrazine monohydrate (2.5 mL, 51.4 mmol) and the resulting mixture was stirred at room temperature for 24 h. Volatile components were evaporated *in vacuo* and the residue was purified by flash CC (EtOAc/MeOH = 10:1). Fractions containing the products were combined and volatile components evaporated *in vacuo* to give the crude mixture of products **5/5'** in a ratio of 1:0.62, respectively, and in 100% conversion. The residue was re-purified by CC (EtOAc/MeOH = 15:1). Fractions containing the products **5/5'** were combined and volatile components evaporated *in vacuo*. Yield: 1.41 g (57%; **5**:**5'** = 1:0.43) of dirty yellow oil. $[\alpha]_D^{r.t.}$ = –26.3 (c = 0.28, $CHCl_3$). EI-HRMS: *m/z* = 340.1653 (MH^+); $C_{19}H_{22}N_3O_3$ requires: *m/z* = 340.1656 (MH^+); ν_{max} 3358, 3280, 3248, 3064, 3032, 2932, 1693, 1682, 1658, 1530, 1496, 1453, 1317, 1246, 1143, 1131, 1082, 1050, 1028, 975, 935, 899, 770, 736, 696, 649 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6) for **5**: δ 2.18 (*dd*, *J* = 16.3; 6.0 Hz, Ha-C (4)); 2.37 (*dd*, *J* = 16.2; 7.9 Hz, Hb-C(4)); 2.56 (*dd*, *J* = 13.8; 10.3 Hz, Ha-C(7)); 3.00 (*dd*, *J* = 13.7; 3.2 Hz, Hb-C(7)); 3.39–3.46 (*m*, H-C(5)); 3.66–3.75 (*m*, H-C(6)); 4.90 (*d*, *J* = 12.9 Hz, Ha of CH_2); 4.97 (*d*, *J* = 12.9, Hb of CH_2); 5.45 (*d*, *J* = 7.5 Hz, H-N(1)); 7.14–7.37 (*m*, 10H of Ph, NH); 9.08 (*s*, H-N(2)). ^{1}H-NMR (500 MHz, DMSO-d_6) for **5'**: δ 2.24 (*dd*, *J* = 16.4; 7.4 Hz, Ha-C(4)); 2.61 (*dd*, *J* = 13.6; 10.4 Hz, Ha-C(7)); 2.83 (*dd*, *J* = 13.7; 4.3 Hz, Hb-C(7)); 3.54–3.62 (*m*, H-C(5)); 3.77–3.84 (*m*, H-C(6)); 4.91 (*d*, *J* = 12.8 Hz, Ha of CH_2); 4.97 (*d*, *J* = 12.8 Hz, Hb of CH_2); 5.28 (*d*, *J* = 7.4 Hz, H-N(1)); 9.01 (*s*, H-N(2)). ^{13}C-NMR (126 MHz, $CDCl_3$) for **5** and **5'**: δ 34.1, 34.5, 36.1, 37.0, 54.2, 54.8, 59.4, 60.2, 64.9, 65.0, 125.9, 126.1, 127.2, 127.3, 127.6, 128.0, 128.1, 128.3, 129.1, 129.2, 137.2, 137.3, 138.8, 138.9, 156.0, 156.1, 175.01, 175.03.

Benzyl ((*S*)-1-((*S*)-2-methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl) carbamate (6'), benzyl ((*S*)-1-((*R*)-2-methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)carbamate (6), benzyl ((*S*)-1-((*R*)-1-methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)carbamate (7), and benzyl ((*S*)-1-((*S*)-1-methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)-carbamate (7'). To a solution of mesylate **4** (4.25 g, 9.75 mmol) in CH_2Cl_2 (60 mL) was added methylhydrazine (4.21 mL, 80 mmol) and the resulting mixture was stirred at room temperature for 24 h. Volatile components were evaporated *in vacuo* and the residue was purified by flash CC (EtOAc/MeOH = 15:1). Fractions containing all the products were combined and volatile components evaporated *in vacuo* to give the crude mixture of products **6/6'/7/7'** in a ratio of 1:0.74:0.73:0.38, respectively, and in 100% conversion. The residue was separated by MPLC (EtOAc/MeOH = 20:1) to give separately a mixture of **6/6'** in a ratio of 1:0.74, pure **7**, and a mixture of **7/7'** in a ratio of 1:0.74, respectively. Fractions containing the separated compounds/mixtures were combined and volatile components evaporated *in vacuo*, respectively.

Compound **7**: Elutes second. Yield: 360 mg (10%) of white solid; mp 146-148 °C. $[\alpha]_D^{r.t.}$ = –38.6 (c = 0.13, $CHCl_3$). ($C_{20}H_{23}N_3O_3$ requires: C, 67.97; H, 6.56; N, 11.89. found C, 67.84; H, 6.47; N, 11.89); EI-HRMS: *m/z* = 354.1812 (MH^+); $C_{20}H_{24}N_3O_3$ requires: *m/z* = 354.1812 (MH^+); ν_{max} 3339, 3208, 3032, 2940, 1689, 1667, 1538, 1494, 1454, 1412, 1398,

1320, 1255, 1221, 1204, 1131, 1085, 1053, 1008, 968, 936, 899, 880, 802, 776, 739, 697, 658 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.27 (*dd*, J = 16.3; 6.1 Hz, Ha-C(4)); 2.46 (*dd*, J = 16.3; 8.2 Hz, Hb-C(4)); 2.55 (*dd*, J = 13.7; 10.3 Hz, Ha-C(7)); 2.85 (*s*, Me-N(2)); 2.95 (*dd*, J = 13.7; 3.4 Hz, Hb-C(7)); 3.31–3.41 (*m*, H-C(5)); 3.62–3.72 (*m*, H-C(6)); 4.90 (*d*, J = 12.9, Ha of CH_2); 4.96 (*d*, J = 12.9 Hz, 1 Hb of CH_2); 5.81 (*d*, J = 8.1 Hz, H-N(1)); 7.14–7.38 (*m*, 10H of Ph, NH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 31.3, 34.0, 37.3, 54.0, 57.0, 67.1, 127.0, 128.1, 128.4, 128.7, 128.8, 129.3, 136.3, 137.0, 156.6, 171.0.

Compound **7'** in a mixture of **7/7'**: Elutes third. Yield: 846 mg (24%, **7**:**7'** = 1:0.74) of white solid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.76 (*dd*, J = 13.7; 4.1 Hz, Ha-C(7)); 2.85 (*s*, Me-N(2)); 3.46–3.54 (*m*, H-C(5)); 3.73–3.80 (*m*, H-C(6)); 5.75 (*d*, J = 8.1 Hz, H-N(1)). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 30.5, 30.6, 34.3, 34.5, 35.9, 36.9, 54.5, 55.1, 55.9, 56.9, 64.95, 64.96, 126.0, 126.1, 127.2, 127.59, 127.62, 128.08, 128.12, 128.29, 128.31, 129.1, 129.2, 137.29, 137.30, 138.81, 138.85, 156.1, 156.2, 170.3, 170.5.

The mixture of epimers **6/6'** was separated by MPLC ($CHCl_3$/MeOH = 60:1). Fractions containing the separated compounds were combined and volatile components evaporated *in vacuo*, respectively.

Compound **6'**: Elutes first. Yield: 642 mg (18%) of white solid; mp 68–69 °C. $[\alpha]_D^{r.t.}$ = –89.5 (c = 0.32, $CHCl_3$). ($C_{20}H_{23}N_3O_3$ requires: C, 67.97; H, 6.56; N, 11.89. found C, 67.10; H, 6.62; N, 11.66); EI-HRMS: m/z = 354.1809 (MH^+); $C_{20}H_{24}N_3O_3$ requires: m/z = 354.1812 (MH^+); ν_{max} 3267, 3176, 3063, 3029, 2955, 2932, 2855, 1701, 1668, 1604, 1533, 1496, 1454, 1397, 1336, 1243, 1127, 1082, 1060, 1026, 954, 927, 740, 695 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.22 (*dd*, J = 17.1; 4.4 Hz, Ha-C(4)); 2.52 (*s*, Me-N(1)); 2.59 (*dd*, J = 13.4; 11.1 Hz, Ha-C(7)); 2.80 (*dd*, J = 17.1; 9.4 Hz, Hb-C(4)); 2.85 (*dd*, J = 13.7; 3.3 , Hb-C(7)); 3.11 (*dt*, J = 9.5; 4.8 Hz, H-C(5)); 3.71–3.78 (*m*, H-C(6)); 4.89 (*d*, J = 13.0 Hz, Ha of CH_2); 4.95 (*d*, J = 12.9 Hz, Hb of CH_2); 7.14–7.34 (*m*, 10H of Ph, NH); 9.32 (*s*, H-N(2)). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 31.2, 35.3, 47.8, 55.4, 64.9, 66.2, 126.0, 127.2, 127.6, 128.1, 128.3, 129.1, 137.3, 138.9, 156.0, 172.00.

Compound **6**: Elutes second. Yield: 869 mg (25%) of white solid; mp 48-51 °C. $[\alpha]_D^{r.t.}$ = –1.0 (c = 0.18, $CHCl_3$). ($C_{20}H_{23}N_3O_3$ requires: C, 67.97; H, 6.56; N, 11.89. found C, 67.49; H, 6.83; N, 11.59); EI-HRMS: m/z = 354.1812 (MH^+); $C_{20}H_{24}N_3O_3$ requires: m/z = 354.1812 (MH^+); ν_{max} 3254, 3061, 3030, 2956, 2925, 2854, 1681, 1604, 1532, 1496, 1454, 1408, 1338, 1247, 1128, 1082, 1050, 1026, 930, 737, 695 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.13 (*dd*, J = 16.9; 4.5 Hz, Ha-C(4)); 2.51 (*s*, Me-N(1)); 2.56 (*dd*, J = 13.7; 10.8 Hz, Ha-C(7)); 2.73 (*dd*, J = 16.9; 8.6 Hz, Hb-C(4)); 2.92–3.02 (*m*, Hb-C(7), H-C(5)); 3.61–3.70 (*m*, H-C(6)); 4.89 (*d*, J = 12.9 Hz, Ha of CH_2); 4.97 (*d*, J = 12.9 Hz, Hb of CH_2); 7.14–7.36 (*m*, 10H of Ph, NH); 9.37 (*s*, H-N(2)). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 31.1, 36.8, 47.1, 53.8, 64.8, 67.7, 126.0, 127.1, 127.6, 128.1, 128.3, 129.0, 137.3, 139.1, 156.1, 172.13.

(*R*)-5-((*S*)-1-Amino-2-phenylethyl)-2-methylpyrazolidin-3-one (8). General Procedure 1 (GP1): Prepared from **7** (335 mg, 0.95 mmol), Pd–C (70 mg), V = 40 mL. Thoroughly dried crude product **8** was used in the following transformations (see the preparation of **9** and **14**). Yield: full conversion; colorless oil. $[\alpha]_D^{r.t.}$ = +0.6 (c = 0.7, MeOH). EI-HRMS: m/z = 220.1446 (MH^+); $C_{12}H_{18}N_3O$ requires: m/z = 220.1444 (MH^+); ν_{max} cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.38 (br *s*, NH_2); 2.31 (*dd*, J = 16.2; 8.2 Hz, Ha-C(4)); 2.43 (*dd*, J = 13.2; 8.5 Hz, Ha-C(7)); 2.50 (*dd*, J = 16.0; 8.4 Hz, Hb-C(4)); 2.71 (*dd*, J = 13.2; 5.0 Hz, Hb-C(7)); 2.81–2.87 (*m*, Me-N(2), H-C(6)); 3.19–3.26 (*m*, H-C(5)); 5.63 (*d*, J = 8.8 Hz, H-N(1)); 7.14–7.25 (*m*, 3H of Ph); 7.25–7.32 (*m*, 2H of Ph). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 30.5, 32.9, 40.7, 53.9, 57.9, 125.9, 128.2, 129.2, 139.5, 170.8.

(*R*)-5-((*S*)-1-Amino-2-phenylethyl)-2-methylpyrazolidin-3-one (8') and (*S*)-5-((*S*)-1-amino-2-phenylethyl)-2-methylpyrazolidin-3-one (8'). General Procedure 1 (GP1): Prepared from a mixture of epimers **7/7'** (353 mg, 1 mmol, **7**:**7'** = 1:0.74), Pd–C (80 mg), V = 40 mL. Thoroughly dried crude mixture of products **8/8'** was used in the following transformations (see the preparation of **9** and **9'**). Yield: full conversion (**8**:**8'** = 1:0.74); colorless oil. ^{1}H-NMR (500 MHz, DMSO-d_6) for **8'**: δ 5.74 (br s, H-N(1). ^{13}C-NMR (126 MHz, DMSO-d_6) for **8'**: δ 30.5, 32.9, 40.4, 54.9, 57.0, 126.0, 128.2, 129.3, 139.5, 170.6.

(3a*R*,4*S*)-4-Benzyl-1-methyltetrahydro-1*H*-imidazo[1,5-*b*]pyrazole-2,6-dione (9). To a solution of crude diamine **8** (85 mg, 0.388 mmol) in anhydrous DMF (10 mL) under argon was added CDI (84 mg, 0.465 mmol) and the resulting mixture was stirred at room temperature for 6 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC (EtOAc). Fractions containing the product **9** were combined and volatile components evaporated *in vacuo*. Yield: 80 mg (84%) of white solid; mp 194–195 °C. $[\alpha]_D^{r.t.}$ = +7.5 (c = 0.08, $CHCl_3$). ($C_{13}H_{15}N_3O_2$ requires: C, 63.66; H, 6.16; N, 17.13. found C, 63.43; H, 6.32; N, 16.94); EI-HRMS: m/z = 246.1239 (MH^+); $C_{13}H_{16}N_3O_2$ requires: m/z = 246.1237 (MH^+); ν_{max} 3217, 3142, 2991, 2959, 2913, 2847, 1732, 1675, 1495, 1477, 1456, 1435, 1415, 1373, 1349, 1327, 1300, 1279, 1251, 1170, 1153, 1118, 1089, 1069, 1018, 962, 895, 858, 828, 805, 763, 724, 699, 628, 605 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.03 (*dd*, J = 16.1; 7.1 Hz, Ha-C(4)); 2.77 (*dd*, J = 14.0; 8.1 Hz, Ha-C(7)), 2.92 (*dd*, J = 14.0; 6.2 Hz, Hb-C(7)); 3.01 (*dd*, J = 16.1; 11.4 Hz, Hb-C(4)); 3.10 (*s*, Me-N(2)); 4.12–4.18 (*m*, H-C(6)); 4.18–4.24 (*m*, H-C(5)); 7.20–7.34 (*m*, 5H of Ph); 7.93 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 30.4, 32.4, 36.3, 51.4, 60.3, 126.6, 128.5, 128.9, 137.0, 163.7, 170.2.

(3a*R*,4*S*)-4-Benzyl-1-methyltetrahydro-1*H*-imidazo[1,5-*b*]pyrazole-2,6-dione (9) and (3a*S*,4*S*)-4-benzyl-1-methyltetrahydro-1*H*-imidazo[1,5-*b*]pyrazole-2,6-dione (9'). To a solution of crude epimere mixture **8/8'** (166 mg, 0.757 mmol; **8**:**8'** = 1:0.75) in anhydrous DMF (10 mL) under argon was added CDI (164 mg, 0.908 mmol) and the resulting mixture was stirred at room temperature for 6 h. Volatile components were evaporated *in vacuo* and the residue was purified by flash CC (EtOAc). Fractions containing both products were combined and volatile components evaporated *in vacuo*. The products were separated by MPLC (EtOAc/petroleum ether = 2:1). Fractions containing the separated products were combined and volatile components evaporated *in vacuo* to give **9** and **9'**, respectively.

Compound **9**: Elutes first. Yield: 92 mg (49%) of white solid. For properties see synthesis of **9**.

Compound **9'**: Elutes second. Yield: 30 mg (16%) of white semisolid. $[\alpha]_D^{r.t.}$ = –147.7 (c = 0.22, $CHCl_3$). ($C_{13}H_{15}N_3O_2$ requires: C, 63.66; H, 6.16; N, 17.13. found C, 63.75; H, 6.53; N, 15.57); EI-HRMS: m/z = 246.123 (MH^+); $C_{13}H_{16}N_3O_2$ requires: m/z = 246.1237 (MH^+); ν_{max} 3255, 3029, 2924, 1731, 1681, 1603, 1494, 1413, 1379, 1299, 1247, 1139, 1084, 1062,

1011, 918, 892, 863, 798, 761, 720, 699, 611 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.32 (*dd*, J = 16.4, 7.8 Hz, Ha-C(4)); 2.68 (*dd*, J = 16.3; 10.9 Hz, Hb-C(4)); 2.81 (*d*, J = 6.7 Hz, H_2-C(7)); 3.09 (*s*, Me-N(2)); 3.80 (*t*, J = 6.7 Hz, H-C(6)); 4.09 (*dd*, J = 10.7; 8.0 Hz, H-C(5)); 7.21–7.27 (*m*, 3H of Ph); 7.28–7.34 (*m*, 2H of Ph); 7.99 (s, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 32.3, 35.1, 40.9, 54.7, 60.0, 126.6, 128.4, 129.3, 137.0, 164.0, 169.8.

Benzyl ((*S*)-1-((*R*)-1,2-dimethyl-5-oxopyrazolidin-3-yl)-2-phenylethyl) carbamate (10). To a solution of **6** (480 mg, 1.36 mmol) in anhydrous DMF (10 mL) under argon was added *t*BuOK (153 mg, 1.36 mmol) followed by addition of MeI (85 μL, 0.833 mmol) and the resulting mixture was stirred at room temperature for 2 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC (EtOAc). Fractions containing the product **10** were combined and volatile components evaporated *in vacuo*. Yield: 458 mg (91%) of colorless oil. $[\alpha]_D^{r.t.}$ = –6.0 (c = 0.15, $CHCl_3$). EI-HRMS: *m/z* = 368.1967 (MH^+); $C_{21}H_{26}N_3O_3$ requires: *m/z* = 368.1969 (MH^+); ν_{max} 3293, 3062, 3030, 2928, 2857, 1666, 1534, 1496, 1454, 1418, 1394, 1339, 1315, 1247, 1185, 1136, 1083, 1044, 964, 915, 739, 697, 640 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.19 (*dd*, J = 16.9; 2.9 Hz, Ha-C(4)); 2.51–2.59 (*m*, Me-N(1), Ha-C(7)); 2.84 (*s*, Me-N(2)); 2.89 (*dd*, J = 16.9; 8.5 Hz, Hb-C(4)); 2.95–3.03 (*m*, Hb-C(7), H-C(5)); 3.57–3.64 (*m*, H-C(6)); 4.91 (*d*, J = 12.9 Hz, Ha of CH_2); 4.95 (*d*, J = 13.1 Hz, Hb of CH_2); 7.15–7.35 (*m*, 10H of Ph, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 28.7, 30.6, 36.6, 43.2, 54.5, 64.9, 65.1, 126.0, 127.2, 127.6, 128.1, 128.3, 129.1, 137.3, 139.1, 156.1, 169.3.

Benzyl ((*S*)-1-((*S*)-1,2-dimethyl-5-oxopyrazolidin-3-yl)-2-phenylethyl) carbamate (10'). To a solution of **6'** (294 mg, 0.833 mmol) in anhydrous DMF (10 mL) under argon was added *t*BuOK (94 mg, 0.833 mmol) followed by addition of MeI (52 μL, 0.833 mmol) and the resulting mixture was stirred at room temperature for 2 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC (EtOAc). Fractions containing the product **10'** were combined and volatile components evaporated *in vacuo*. Yield: 250 mg (81%) of white solid; mp 143–149 °C. $[\alpha]_D^{r.t.}$ = –80.3 (c = 0.28, $CHCl_3$). ($C_{21}H_{25}N_3O_3$ requires: C, 68.64; H, 6.86; N, 11.44. found C, 67.92; H, 6.46; N, 11.40); EI-HRMS: *m/z* = 368.1968 (MH^+); $C_{21}H_{26}N_3O_3$ requires: *m/z* = 368.1969 (MH^+); ν_{max} 3302, 3059, 3031, 2952, 2856, 2789, 1716, 1682, 1603, 1533, 1496, 1454, 1411, 1386, 1364, 1328, 1249, 1121, 1087, 1042, 1025, 970, 935, 912, 848, 746, 697 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.26 (*dd*, J = 16.8; 2.6 Hz, Ha-C(4)); 2.56 (*s*, Me-N(1)); 2.60 (*dd*, J = 13.9; 10.8 Hz, Ha-C(7)); 2.76 (*dd*, J = 14.1; 3.8 Hz, Hb-C(7)); 2.83 (*s*, Me-N(2)); 2.96 (*dd*, J = 16.9; 9.3 Hz, Hb-C(4)); 3.09–3.15 (*m*, H-C(5)); 3.66–3.75 (*m*, H-C(6)); 4.91 (*d*, J = 12.9 Hz, Ha of CH_2); 4.95 (*d*, J = 13.0 Hz, Hb of CH_2); 7.15–7.34 (*m*, 10H of Ph, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 28.5, 30.8, 35.3, 43.7, 55.6, 63.9, 64.8, 126.0, 127.1, 127.5, 128.1, 128.3, 129.1, 137.4, 138.9, 156.3, 169.3.

Benzyl ((*S*)-1-((*R*)-1,2-dimethyl-5-oxopyrazolidin-3-yl)-2-phenylethyl) carbamate (10). To a solution of **7** (100 mg, 0.283 mmol) in MeOH (5 mL) were added HCHO (1.26 mL, 17 mmol, ω = 37% in H_2O) and AcOH (100 μL, 1.747 mmol). After stirring at room temperature for 1 h, $NaCNBH_3$ (113 mg, 1.7 mmol) was added and the resulting mixture was stirred for 1 h at room temperature. Volatile components were evaporated *in vacuo*, the residue was suspended in CH_2Cl_2 (150 mL), and washed with $NaHCO_3$ (aq. sat., 10 mL), and NaCl (aq. sat., 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated *in vacuo*. The residue was purified by flash CC (EtOAc). Fractions containing the crude product **10** were combined and volatile components evaporated *in vacuo*. Yield: 43 mg (41%) of colorless oil.

(*R*)-*tert*-Butyl 5-((*S*)-1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-3-oxopyrazolidine-1-carboxylate (11) and (*S*)-*tert*-butyl 5-((*S*)-1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-3-oxopyrazolidine-1-carboxylate (11'). To a suspension of epimeres **5/5'** (340 mg, 1 mmol, **5**:**5'** = 1:0.43) in anhydrous CH_2Cl_2 (25 mL) were added Et_3N (140 μL, 1 mmol) and Boc_2O (218 mg, 1 mmol) and the resulting mixture was stirred at room temperature for 2 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC (EtOAc/petroleum ether = 1:1). Fractions containing the products were combined and volatile components evaporated *in vacuo* to give the mixture of products **11/11'** in a ratio of 1:0.5, respectively. Yield: 240 mg (54%; **11**:**11'** = 1:0.5) of white solid; mp 63-71 °C. $[\alpha]_D^{r.t.}$ = +9.3 (c = 0.08, $CHCl_3$). ($C_{24}H_{29}N_3O_5$ requires: C, 65.59; H, 6.65; N, 9.56. found C, 65.32; H, 6.33; N, 9.50). ν_{max} 3306, 3064, 3030, 2978, 2934, 1687, 1527, 1496, 1454, 1367, 1327, 1242, 1157, 1121, 1083, 1047, 1028, 855, 739, 697 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6) for **11**: δ 1.43 (*s*, *t*Bu); 2.38 (*d*, J = 17.3 Hz, Ha-C(4)); 2.62 (*dd*, J = 13.6; 10.5 Hz, Ha-C(7)); 2.78 (*dd*, J = 14.1; 4.1 Hz, Hb-C(7)); 2.88 (*dd*, J = 17.1; 10.0 Hz, Hb-C(4)); 3.86–3.97 (*m*, H-C(6)); 4.25–4.33 (*m*, H-C(5)); 4.87 (*d*, J = 12.8 Hz, Ha of CH_2); 4.98 (*d*, J = 12.9 Hz, Hb of CH_2); 7.13–7.35 (*m*, 10H of Ph); 7.44 (*d*, J = 9.4 Hz, NH); 10.49 (*s*, H-N(2)). ^{1}H-NMR (500 MHz, DMSO-d_6) for **11'**: δ 1.46 (*s*, *t*Bu); 2.95 (*dd*, J = 17.3; 10.2 Hz, Hb-C(4)); 4.43–4.48 (*m*, H-C(5)); 4.86 (*d*, J = 12.9 Hz, Ha of CH_2); 4.95 (*d*, J = 13.2 Hz, Hb of CH_2); 10.39 (*s*, H-N(2)). ^{13}C-NMR (126 MHz, $CDCl_3$) for **11** and **11'**: δ 27.88, 27.93, 32.0, 32.4, 34.6, 36.4, 54.7, 55.4, 59.6, 59.8, 64.9, 65.0, 80.9, 81.0, 126.07, 126.12, 127.1, 127.2, 127.5, 127.6, 128.1, 128.2, 128.27, 128.29, 129.0, 137.1, 137.2, 138.5, 138.7, 154.1, 154.2, 156.0, 156.1, 170.4, 170.7.

(*R*)-*tert*-Butyl 5-((*S*)-1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-2-methyl-3-oxopyrazolidine-1-carboxylate (12) and (*S*)-*tert*-butyl 5-((*S*)-1-(((benzyloxy)-carbonyl)amino)-2-phenylethyl)-2-methyl-3-oxopyrazolidine-1-carboxylate (12'). To a solution of epimeres **11/11'** (180 mg, 0.41 mmol, **11**:**11'** = 1:0.5) in anhydrous DMF (10 mL) were added K_2CO_3 (57 mg, 0.41 mmol) and MeI (77 μL, 1.23 mmol) and the resulting mixture was stirred at room temperature for 24 h. Volatile components were evaporated *in vacuo* and the residue was purified by CC (EtOAc/petroleum ether = 1:1). Fractions containing the products were combined and volatile components evaporated *in vacuo* to give the mixture of products **12/12'** in a ratio of 1:0.5, respectively. Yield: 181 mg (97%; **12**:**12'** = 1:0.5) of colorless oil. $[\alpha]_D^{r.t.}$ = –16.3 (c = 0.19, $CHCl_3$). EI-HRMS: *m/z* = 454.2332 (MH^+); $C_{25}H_{32}N_3O_5$ requires: *m/z* = 454.2336 (MH^+). ν_{max} 3315, 2978, 2932, 1690, 1530, 1497, 1455, 1415, 1393, 1368, 1324, 1294, 1240, 1160, 1143, 1109, 1045, 1029, 850, 737, 697, 674 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6) for **12**: δ 1.44 (*s*, *t*Bu); 2.36 (*dd*, J = 16.9; 10.4 Hz, Ha-C(4)); 2.62 (*dd*, J = 13.7; 10.0 Hz, Ha-C(7)); 2.76–2.83 (*m*, Hb-C(7)); 2.97 (*s*, Me-N(2)); 3.00 (*dd*, J = 17.6; 9.9 Hz, Hb-C(4)); 3.75–3.87 (*m*, H-C(6)); 4.36 (*dd*, J = 8.7; 6.3 Hz, H-C(5)); 4.94 (*s*, CH_2); 7.14 (*d*, J = 6.8 Hz, 1H of Ph); 7.19–7.36 (*m*, 9H of Ph); 7.46 (*d*, J = 9.2 Hz, NH). ^{1}H-NMR (500 MHz,

DMSO-d_6) for **12'**: δ 1.48 (*s*, *t*Bu); 2.68 (*dd*, J = 13.9; 11.7 Hz, Ha-C(7)); 4.47 (*dd*, J = 9.1; 3.8 Hz, H-C(5)); 4.91 (*d*, J = 13.0 Hz, Ha of CH_2); 4.94 (*d*, J = 12.9 Hz, Hb of CH_2). ^{13}C-NMR (126 MHz, $CDCl_3$) for **12** and **12'**: δ 27.77, 27.80, 31.7, 33.0, 33.1, 33.2, 35.9, 36.1, 55.1, 55.7, 60.3, 61.2, 64.9, 65.1, 81.7, 81.8, 126.06, 126.13, 127.0, 127.4, 127.5, 127.7, 128.0, 128.16, 128.23, 128.3, 129.1, 137.0, 137.2, 138.5, 138.7, 155.8, 156.0, 156.4, 156.5, 170.3, 171.0.

Benzyl ((*S*)-1-((*R*)-1-methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl) carbamate (7) and benzyl ((*S*)-1-((*S*)-1-methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)-carbamate (7'). To a solution of epimeres **12/12'** (90 mg, 0.2 mmol, **12**:**12'** = 1:0.5) in anhydrous CH_2Cl_2 (5 mL) was added TFA (3 mL) and the resulting mixture was stirred at room temperature for 5 h. Volatile components were evaporated *in vacuo*, the residue was dissolved in EtOAc (150 mL) and washed with $NaHCO_3$ (aq. sat., 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated *in vacuo* to give crude mixture of epimers **7/7'** in a ratio of 1:0.48, respectively. Yield: 46 mg (66%) of white solid.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-1-((*R*)-1-methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)thiourea (14). General Procedure 2 (GP2): Prepared from **8** (39 mg, 0.178 mmol), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**13**) (33 μL, 0.178 mmol), V(Et_2O) = 10 mL, CC (1. EtOAc/petroleum ether = 1:1 (to elute the less polar impurities); 2. EtOAc (to elute the product **14**)). Yield: 56 mg (64%) of white solid; mp 90–93 °C. $[\alpha]_D^{r.t.}$ = –74.1 (c = 0.085, $CHCl_3$). ($C_{21}H_{20}F_6N_4OS$ requires: C, 51.43; H, 4.11; N, 11.42. found C, 48.16; H, 3.62; N, 10.57); EI-HRMS: m/z = 491.1335 (MH^+); $C_{21}H_{21}F_6N_4OS$ requires: m/z = 491.1335 (MH^+); ν_{max} 3289, 3202, 3065, 2930, 1666, 1538, 1496, 1472, 1456, 1383, 1339, 1275, 1170, 1125, 1031, 1001, 959, 934, 884, 848, 727, 699, 680, 656 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.43 (*dd*, J = 16.5; 4.9 Hz, Ha-C(4)); 2.60 (*dd*, J = 16.4; 8.7 Hz, Hb-C(4)); 2.75 (*dd*, J = 13.8; 9.3 Hz, Ha-C(7)); 2.89 (*s*, Me-N(2)); 2.98 (*dd*, J = 14.2; 4.2 Hz, Hb-C(7)); 3.55–3.65 (*m*, H-C(5)); 4.70–4.79 (*m*, H-C(6)); 5.97 (*d*, J = 7.8 Hz, H-N(1)); 7.14–7.33 (*m*, 5H of Ph); 7.73 (*s*, 1H of Arl); 8.15 (*s*, 2H of Arl); 8.20 (*d*, J = 8.8 Hz, NH); 9.96 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 30.5, 34.3, 35.4, 55.3, 56.8, 116.3, 122.0, 123.2 (*q*, J = 272.6 Hz), 126.2, 128.1, 129.2, 130.2 (*q*, J = 32.7 Hz), 138.0, 141.6, 170.3, 180.6.

(*R*)-5-((*S*)-1-Amino-2-phenylethyl)-1-methylpyrazolidin-3-one (15) and (*S*)-5-((*S*)-1-amino-2-phenylethyl)-1-methylpyrazolidin-3-one (15'). General Procedure 1 (GP1): Prepared from a mixture of epimers **6/6'** (354 mg, 1 mmol, **6**:**6'** = 1:0.74), Pd–C (70 mg), V = 40 mL. Thoroughly dried crude mixture of products **15/15'** was used in the following transformation (see the preparation of **16** and **16'**) without any characterization.

(*R*)-5-((*S*)-1-Amino-2-phenylethyl)-1-methylpyrazolidin-3-one (15). General Procedure 1 (GP1): Prepared from **6** (213 mg, 0.60 mmol), Pd–C (50 mg), V = 30 mL. Thoroughly dried crude product **15** was used in the following transformation (see the preparation of **16**). Yield: full conversion; colorless oil. $[\alpha]_D^{r.t.}$ = +98.9 (c = 0.55, MeOH). EI-HRMS: m/z = 220.1449 (MH^+); $C_{12}H_{18}N_3O$ requires: m/z = 220.1444 (MH^+); ν_{max} 3350, 3178, 3061, 3027, 2959, 2918, 2856, 2795, 1668, 1601, 1494, 1454, 1411, 1346, 1180, 1103, 1078, 1029, 918, 793, 744, 701 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.39 (*dd*, J = 13.4; 8.8 Hz, Ha-C(7)); 2.43 (*s*, Me-N(1)); 2.45–2.57 (*m*, H_2-C(4)); 2.70 (*dd*, J = 13.3; 4.9 Hz, Hb-C(7)); 2.69–2.76 (*m*, H-C(5)); 2.96 (*dt*, J = 9.1; 4.9 Hz, H-C(6)); 3.35 (br *s*, NH_2); 7.09–7.35 (*m*, 5H of Ph); 9.28 (br *s*, H-N(2)). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 30.0, 39.8, 46.5, 53.1, 69.1, 125.9, 128.2, 129.1, 139.6, 172.0.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-1-((*S*)-2-methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)thiourea (16') and 1-(3,5-bis (trifluoromethyl)phenyl)-3-((*S*)-1-((*R*)-2-methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)thiourea (16). General Procedure 2 (GP2): Prepared from a mixture of crude amine epimers **15/15'** (220 mg, 1 mmol; **15**:**15'** = 1:0.74), 3,5-bis(trifluoromethyl)-phenyl isothiocyanate (**13**) (186 μL, 1 mmol), V(CH_2Cl_2) = 20 mL, MPLC ($CHCl_3$/EtOH = 20:1).

Compound **16'**: Elutes first. Yield: 120 mg (24%) of white solid; mp 85-91 °C. $[\alpha]_D^{r.t.}$ = –78.9 (c = 0.19, $CHCl_3$). ($C_{21}H_{20}F_6N_4OS$ requires: C, 51.43; H, 4.11; N, 11.42. found C, 50.95; H, 3.62; N, 11.09); EI-HRMS: m/z = 491.1331 (MH^+); $C_{21}H_{21}F_6N_4OS$ requires: m/z = 491.1335 (MH^+); ν_{max} 3217, 3063, 2925, 2854, 1678, 1527, 1472, 1456, 1381, 1340, 1274, 1170, 1124, 999, 966, 941, 885, 847, 698, 680 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.24 (*dd*, J = 17.2; 4.5 Hz, Ha-C(4)); 2.58 (*s*, Me-N(1)); 2.78–2.92 (*m*, Hb-C(4), Ha-C(7)); 2.98 (*dd*, J = 14.0; 5.7 Hz, Hb-C(7)); 3.27–3.33 (*m*, H-C(5)); 4.73–4.83 (*m*, H-C(6)); 7.18–7.24 (*m*, 1H of Ph); 7.26–7.34 (*m*, 4H of Ph); 7.74 (*s*, 1H of Arl); 8.04 (*d*, J = 8.8 Hz, NH); 8.20 (*s*, 2H of Arl); 9.37 (*s*, NH); 10.16 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 31.6, 35.9, 48.0, 57.9, 64.3, 116.3, 121.9, 123.2 (*q*, J = 272.7 Hz), 126.3, 128.3, 129.0, 130.2 (*q*, J = 32.7 Hz), 138.2, 141.6, 171.6, 180.8.

Compound **16**: Elutes second. Yield: 120 mg (24%) of white solid; mp 89-96 °C. $[\alpha]_D^{r.t.}$ = –13.6 (c = 0.12, $CHCl_3$). ($C_{21}H_{20}F_6N_4OS$ requires: C, 51.43; H, 4.11; N, 11.42. found C, 52.78; H, 4.24; N, 10.67); EI-HRMS: m/z = 491.1335 (MH^+); $C_{21}H_{21}F_6N_4OS$ requires: m/z = 491.1335 (MH^+); ν_{max} 3231, 3065, 2924, 2854, 1682, 1531, 1497, 1472, 1456, 1381, 1275, 1170, 1125, 1001, 986, 965, 883, 847, 726, 698, 680 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.26 (*dd*, J = 17.2, 3.7 Hz, Ha-C(4)); 2.53 (*s*, Me-N(1)); 2.76–2.90 (*m*, Ha-C(7), Hb-C(4)); 3,02 (*dd*, J = 13.8; 2.7 Hz, Hb-C(7)); 3.14–3.22 (*m*, H-C(5)); 4.72–4.81 (*m*, H-C(6)); 7.15–7.23 (*m*, 1H of Ph); 7.25–7.33 (*m*, 4H of Ph); 7.73 (*s*, 1H of Arl); 8.16 (*s*, 2H of Arl); 8.24 (*d*, J = 8.9 Hz, NH); 9.47 (*s*, NH); 9.97 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 31.1, 35.7, 47.6, 56.3, 66.3, 116.2, 121.9, 123.2 (*q*, J = 272.8 Hz), 126.2, 128.2, 129.1, 130.2 (*q*, J = 32.8 Hz), 138.2, 141.6, 172.1, 180.6.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-1-((*R*)-2-methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)thiourea (16). General Procedure 2 (GP2): Prepared from crude amine **15** (29 mg, 0.132 mmol), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**13**) (25 μL, 0.132 mmol), V(Et_2O) = 10 mL, CC ($CHCl_3$/EtOH = 30:1). Yield: 48 mg (75%) of white solid.

(*R*)-5-((*S*)-1-Amino-2-phenylethyl)-1,2-dimethylpyrazolidin-3-one (17). General Procedure 1 (GP1): Prepared from **10** (221 mg, 0.60 mmol), Pd–C (50 mg), V = 30 mL. Thoroughly dried crude product **10** was used in the following transformations (see the preparation of **18**) without any characterization. Yield: full conversion; colorless oil.

(*S*)-5-((*S*)-1-Amino-2-phenylethyl)-1,2-dimethylpyrazolidin-3-one (17'). General Procedure 1 (GP1): Prepared from **10'** (142 mg, 0.386 mmol), Pd–C (40 mg), V = 30 mL. Thoroughly dried crude product **10'** was used in the following transformations (see the preparation of **18'**) without any characterization. Yield: full conversion; colorless oil.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-1-((*R*)-1,2-dimethyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)thiourea (18). General Procedure 2 (GP2): Prepared from **17** (140 mg, 0.6 mmol), 3,5-bis (trifluoromethyl)phenyl isothiocyanate (**13**) (112 μL, 0.6 mmol), V(Et_2O) = 20 mL, CC (EtOAc). Yield: 180 mg (59%) of white solid; mp 185–190 °C. $[\alpha]_D^{r.t.}$ = –45.0 (c = 0.12, $CHCl_3$). ($C_{22}H_{22}F_6N_4OS$ requires: C, 52.38; H, 4.40; N, 11.11. found C, 52.20; H, 4.33; N, 11.00); EI-HRMS: *m/z* = 505.1498 (MH^+); $C_{22}H_{23}F_6N_4OS$ requires: *m/z* = 505.1491 (MH^+); ν_{max} 3292, 3101, 2934, 1658, 1635, 1601, 1523, 1473, 1455, 1385, 1338, 1273, 1229, 1182, 1123, 999, 970, 962, 925, 895, 880, 848, 754, 728, 698, 679, 644 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.33 (*dd*, *J* = 17.1; 2.9 Hz, Ha-C (4)); 2.59 (*s*, Me-N(1)); 2.71 (*dd*, *J* = 14.1; 9.8 Hz, Ha-C(7)); 2.89 (*s*, Me-N(2)); 2.93–3.05 (*m*, Hb-C(7), Hb-C(4)); 3.24–3.31 (*m*, H-C(5)); 4.61–4.74 (*m*, H-C(6)); 7.14–7.22 (*m*, 1H of Ph); 7.23–7.34 (*m*, 4H of Ph); 7.73 (*s*, 1H of Arl); 8.16 (*s*, 2H of Arl); 8.21 (*d*, *J* = 8.7 Hz, NH); 10.00 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 28.5, 30.9, 35.1, 43.6, 56.9, 63.9, 116.2, 121.84, 123.2 (*q*, *J* = 272.9 Hz), 126.1, 128.1, 129.1, 130.2 (*q*, *J* = 32.6 Hz), 138.2, 141.6, 169.2, 180.5.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-1-((*S*)-1,2-dimethyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)thiourea (18'). General Procedure 2 (GP2): Prepared from **17'** (90 mg, 0.386 mmol), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**13**) (72 μL, 0.386 mmol), V(Et_2O) = 20 mL, CC (EtOAc). Yield: 120 mg (61%) of white solid; mp 86-92 °C. $[\alpha]_D^{r.t.}$ = –98.4 (c = 0.062, $CHCl_3$). ($C_{22}H_{22}F_6N_4OS$ requires: C, 52.38; H, 4.40; N, 11.11. found C, 52.28; H, 4.12; N, 10.82); EI-HRMS: *m/z* = 505.1489 (MH^+); $C_{22}H_{23}F_6N_4OS$ requires: *m/z* = 505.1491 (MH^+); ν_{max} 3306, 3091, 2928, 2857, 1656, 1603, 1530, 1473, 1456, 1421, 1383, 1336, 1274, 1170, 1123, 1031, 1000, 969, 941, 881, 847, 729, 698, 679 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.36 (*dd*, *J* = 16.7; 3.1 Hz, Ha-C(4)); 2.62 (*s*, Me-N(1)); 2.83 (*dd*, *J* = 14.0; 9.0 Hz, Ha-C(7)); 2.90 (*m*, 4H, Me-N(2), Hb-C(7)); 2.97 (*dd*, *J* = 17.0; 9.5 Hz, Hb-C(4)); 3.31–3.38 (*m*, H-C(5)); 4.78–4.87 (*m*, H-C(6)); 7.17–7.24 (*m*, 1H of Ph); 7.26–7.34 (*m*, 4H of Ph); 7.74 (*s*, 1H of Arl); 7.89 (*d*, *J* = 9.0 Hz, NH); 8.17 (*s*, 2H of Arl); 10.07 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 28.6, 31.1, 35.8, 43.8, 57.8, 62.3, 116.4, 122.1, 123.2 (*q*, *J* = 272.7 Hz), 126.3, 128.3, 129.0, 130.2 (*q*, *J* = 32.7 Hz), 138.1, 141.6, 169.0, 180.9.

1-((*S*)-1-((*R*)-2-Methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)-3-(naphthalen-1-yl)thiourea (20). General Procedure 2 (GP2): Prepared from crude amine **15** (66 mg, 0.30 mmol), 1-isothiocyanatonaphthalene (**19**) (59 mg, 0.30 mmol), V(DMF) = 10 mL, CC (EtOAc). Yield: 60 mg (49%) of white solid; mp 170-173 °C. $[\alpha]_D^{r.t.}$ = –46.7 (c = 0.12, $CHCl_3$). ($C_{23}H_{24}N_4OS$ requires: C, 68.29; H, 5.98; N, 13.85. found C, 67.34; H, 6.15; N, 12.45); EI-HRMS: *m/z* = 405.1737 (MH^+); $C_{23}H_{25}N_4OS$ requires: *m/z* = 405.1744 (MH^+); ν_{max} 3365, 3147, 3056, 2957, 2857, 1698, 1594, 1519, 1494, 1454, 1444, 1389, 1369, 1340, 1266, 1239, 1190, 1079, 1040, 1008, 953, 900, 790, 772, 746, 732, 699, 639 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.26 (*dd*, *J* = 17.0; 2.2 Hz, Ha-C(4)); 2.50 (*s*, Me-N(1)); 2.68 (*dd*, *J* = 13.3; 10.5 Hz, Ha-C(7)); 2.79 (*dd*, *J* = 17.0; 9.0 Hz, Hb-C (4)); 3.01 (*dd*, *J* = 13.7; 2.9 Hz, Hb-C(7)); 3.09–3.17 (*m*, H-C(5)); 4.71–4.79 (*m*, H-C(6)); 7.16–7.25 (*m*, 3H of Arl); 7.26–7.32 (*m*, 3H of Arl); 7.38 (*d*, *J* = 8.9 Hz, NH); 7.45–7.56 (*m*, 3H of Arl); 7.70 (*d*, *J* = 7.8 Hz, 1H of Arl); 7.84 (*d*, *J* = 8.2 Hz, 1H of Arl); 7.95 (*d*, *J* = 7.7 Hz, 1H of Arl); 9.40 (*s*, NH); 9.50 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 31.0, 35.8, 47.8, 56.9, 66.6, 122.8, 125.3, 125.6, 126.0, 126.2, 126.8, 128.0, 128.1, 129.3, 130.0, 133.9, 134.2, 138.5, 172.5, 182.3.

1-((*S*)-1-((*S*)-2-Methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)-3-(naphthalen-1-yl)thiourea (20'). General Procedure 2 (GP2): Prepared from crude amine **15'** (45 mg, 0.204 mmol), 1-isothiocyanatonaphthalene (**19**) (40 mg, 0.204 mmol), V(DMF) = 5 mL, CC (EtOAc). Yield: 42 mg (51%) of white solid; mp 81-87 °C. $[\alpha]_D^{r.t.}$ = –93.0 (c = 0.10, $CHCl_3$). ($C_{23}H_{24}N_4OS$ requires: C, 68.29; H, 5.98; N, 13.85. found C, 67.88; H, 6.75; N, 11.88); EI-HRMS: *m/z* = 405.1737 (MH^+); $C_{23}H_{25}N_4OS$ requires: *m/z* = 405.1744 (MH^+); ν_{max} 3205, 3058, 2957, 2928, 2858, 1662, 1596, 1519, 1494, 1454, 1438, 1388, 1343, 1267, 1247, 1192, 1166, 1094, 1045, 1014, 953, 924, 870, 779, 747, 699, 660, 606 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.30 (*dd*, *J* = 17.2; 4.1 Hz, Ha-C(4)); 2.53 (*s*, Me-N(1)); 2.73–2.84 (*m*, Hb-C(4), Ha-C(7)); 2.88 (*dd*, *J* = 13.8; 5.6 Hz, Hb-C(7)); 3.24–3.30 (*m*, H-C(5)); 4.77–4.86 (*m*, H-C(6)); 7.19–7.26 (*m*, 3H of Arl); 7.26–7.34 (*m*, 3H of Arl, NH); 7.44–7.57 (*m*, 3H of Arl); 7.73 (*d*, *J* = 8.0 Hz, 1H of Arl); 7.84 (*d*, *J* = 8.2 Hz, 1H of Arl); 7.91–7.98 (*m*, 1H of Arl); 9.29 (*s*, NH); 9.64 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 31.4, 36.0, 48.1, 58.4, 64.5, 122.9, 125.0, 125.6, 126.16, 126.21, 126.7, 128.0, 128.2, 129.1, 129.8, 133.9, 134.3, 138.4, 171.9, 182.4.

(*R*)-2-Methyl-5-oxo-*N*-phenyl-3-((*S*)-2-phenyl-1-(3-phenylureido) ethyl)-pyrazolidine-1-carboxamide (23). General Procedure 2 (GP2): Prepared from crude amine **15** (66 mg, 0.30 mmol), phenyl isocyanate (**21**) (36 μL, 0.33 mmol), V(DMF) = 10 mL, CC (EtOAc/petroleum ether = 1:1). Yield: 47 mg (34%) of white solid; mp 173-177 °C. $[\alpha]_D^{r.t.}$ = –101.8 (c = 0.11, $CHCl_3$). ($C_{26}H_{27}N_5O_3$ requires: C, 68.25; H, 5.95; N, 15.31. found C, 68.07; H, 5.69; N, 15.16); EI-HRMS: *m/z* = 458.2182 (MH^+); $C_{26}H_{28}N_5O_3$ requires: *m/z* = 458.2187 (MH^+); ν_{max} 3336, 3057, 3030, 2927, 1761, 1723, 1700, 1651, 1597, 1545, 1497, 1442, 1386, 1310, 1292, 1214, 1190, 1078, 1030, 897, 750, 692 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.61 (*dd*, *J* = 13.8; 10.5 Hz, Ha-C(7)); 2.65 (*d*, *J* = 17.8 Hz, Ha-C(4)); 2.81 (*s*, Me-N(1)); 3.09 (*dd*, *J* = 13.8; 2.7 Hz, Hb-C(7)); 3.28 (*t*, *J* = 7.9 Hz, H-C(5)); 3.54 (*dd*, *J* = 17.9; 8.7 Hz, Hb-C(4)); 3.76–3.88 (*m*, H-C(6)); 6.26 (*d*, *J* = 9.0 Hz, NH); 6.86 (*t*, *J* = 7.3 Hz, 1H of Ph); 7.11 (*t*, *J* = 7.4 Hz, 1H of Ph); 7.14–7.19 (*m*, 3H of Ph); 7.20–7.30 (*m*, 6H of Ph); 7.35 (*t*, *J* = 7.9 Hz, 2H of Ph); 7.54 (*d*, *J* = 7.8 Hz, 2H of Ph); 8.45 (*s*, NH); 10.03 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 32.8, 36.1, 45.7, 52.8, 64.1, 117.6, 119.8, 121.1, 123.9, 126.1, 128.2, 128.6, 129.0, 129.1, 137.4, 138.8, 140.2, 147.0, 154.9, 174.4.

(*R*)-2-methyl-5-oxo-3-((*S*)-2-phenyl-1-(3-(*p*-tolyl)ureido)ethyl)-*N*-(*p*-tolyl)pyra-zolidine-1-carboxamide (24). General Procedure 2 (GP2): Prepared from crude amine **15** (66 mg, 0.30 mmol), c (42 μL, 0.33 mmol), V(DMF) = 10 mL, CC (EtOAc/petroleum ether = 1:1). Yield: 65 mg (44%) of white solid; mp 99–105 °C. $[\alpha]_D^{r.t.}$ = –79.3 (c = 0.14, $CHCl_3$). ($C_{28}H_{31}N_5O_3$ requires: C, 69.26; H, 6.43; N, 14.42. found C, 69.03; H, 7.17; N, 12.10); EI-HRMS: *m/z* = 486.2496 (MH^+); $C_{28}H_{32}N_5O_3$ requires: *m/z* = 486.2500 (MH^+); ν_{max} 3269, 2953, 2921, 2856, 1719, 1651, 1597, 1513, 1454, 1406, 1311, 1286, 1210, 1122,

1030, 811, 736, 699 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.19 (*s*, Me); 2.27 (*s*, Me); 2.57–2.67 (*m*, Ha-C(7), Ha-C (4)); 2.80 (*s*, Me-N(1)); 3.08 (*dd*, *J* = 13.6; 2.3 Hz, Hb-C (7)); 3.26 (*t*, *J* = 8.1 Hz, H-C(5)); 3.52 (*dd*, *J* = 17.8; 8.6 Hz, Hb-C(4)); 3.76–3.85 (*m*, H-C(6)); 6.19 (*d*, *J* = 9.0 Hz, NH); 6.97 (*d*, *J* = 8.3 Hz, 2H of Arl); 7.13–7.19 (*m*, 5H of Arl); 7.19–7.27 (*m*, 4H of Arl); 7.41 (*d*, *J* = 8.3 Hz, 2H of Arl); 8.33 (*s*, NH); 9.97 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 20.3, 20.4, 32.9, 36.2, 45.6, 52.8, 64.1, 117.7, 119.9, 126.0, 128.2, 129.0, 129.1, 129.4, 129.8, 132.9, 134.8, 137.6, 138.8, 147.0, 155.0, 174.4.

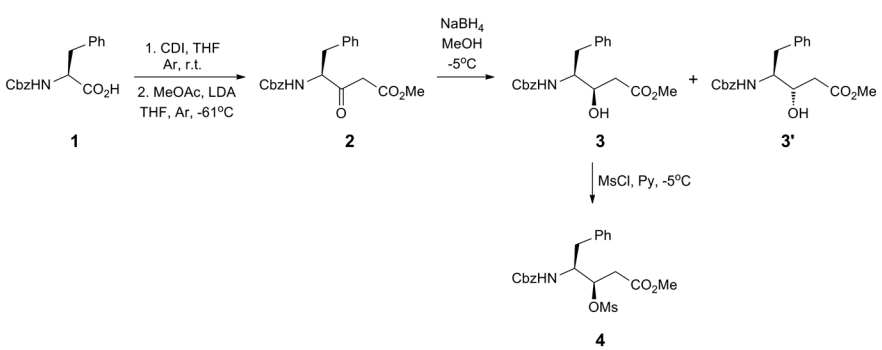
Benzyl ((*S*)-1-((*R*)-1-((4-bromophenyl)carbamoyl)-2-methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)carbamate (26). General Procedure 2 (GP2): Prepared from **6** (71 mg, 0.20 mmol), 4-bromophenyl isocyanate (**25**) (40 mg, 0.20 mmol), V(CH_2Cl_2) = 5 mL, CC (EtOAc/petroleum ether = 1:2). Yield: 70 mg (63%) of white solid; mp 52-55 °C. $[\alpha]_D^{r.t.}$ = –46.0 (c = 0.10, $CHCl_3$). ($C_{27}H_{27}BrN_4O_4$ requires: C, 58.81; H, 4.94; N, 10.16. found C, 58.64; H, 4.81; N, 9.98); EI-HRMS: *m/z* = 551.1285 (MH^+); $C_{27}H_{28}BrN_4O_4$ requires: *m/z* = 551.1288 (MH^+); ν_{max} 3275, 3030, 2925, 1720, 1699, 1591, 1539, 1490, 1454, 1398, 1319, 1302, 1277, 1213, 1190, 1139, 1120, 1072, 1028, 1006, 823, 737, 697 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.50–2.61 (*m*, Ha-C(7), Ha-C(4)); 2.78 (*s*, Me-N(1)); 3.09 (*dd*, *J* = 13.6; 2.8 Hz, Hb-C(7)); 3.20 (*t*, *J* = 7.9 Hz, H-C(5)); 3.48 (*dd*, *J* = 17.9; 8.5 Hz, Hb-C(4)); 3.61–3.69 (*m*, H-C(6)); 4.84 (*d*, *J* = 12.8 Hz, Ha-CH_2); 4.90 (*d*, *J* = 12.8 Hz, Hb-CH_2); 7.12–7.15 (*m*, 2H of Arl); 7.17–7.21 (*m*, 3H of Arl); 7.21–7.32 (*m*, 5H of Arl); 7.44 (*d*, *J* = 9.2 Hz, NH); 7.53 (*s*, 4H of Arl); 9.89 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 32.5, 36.1, 45.6, 54.8, 64.1, 65.1, 115.5, 122.0, 126.0, 127.2, 127.6, 128.1, 128.3, 129.1, 131.7, 136.9, 137.1, 138.8, 147.0, 156.1, 173.7.

Benzyl ((*S*)-1-((*S*)-1-((4-bromophenyl)carbamoyl)-2-methyl-5-oxopyrazolidin-3-yl)-2-phenylethyl)carbamate (26'). General Procedure 2 (GP2): Prepared from **6'** (283 mg, 0.80 mmol), 4-bromophenyl isocyanate (**25**) (160 mg, 0.80 mmol), V(CH_2Cl_2) = 15 mL, CC (EtOAc/petroleum ether = 1:2). Yield: 300 mg (68%) of white solid; mp 62-64 °C. $[\alpha]_D^{r.t.}$ = –20.8 (c = 0.12, $CHCl_3$). ($C_{27}H_{27}BrN_4O_4$ requires: C, 58.81; H, 4.94; N, 10.16. found C, 58.80; H, 4.64; N, 9.88); EI-HRMS: *m/z* = 551.1286 (MH^+); $C_{27}H_{28}BrN_4O_4$ requires: *m/z* = 551.1288 (MH^+); ν_{max} 3330, 3031, 2969, 1716, 1697, 1593, 1543, 1490, 1454, 1398, 1372, 1300, 1278, 1239, 1211, 1175, 1120, 1071, 1042, 1006, 948, 824, 793, 737, 697, 639 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.62–2.72 (*m*, Ha-C(7), Ha-C(4)); 2.76 (*s*, Me-N(1)); 2.85 (*dd*, *J* = 13.7; 3.9 Hz, Hb-C(7)); 3.27–3.33 (*m*, H-C(5)); 3.50 (dd, *J* = 17.7; 8.8 Hz, Hb-C(4)); 3.77–3.85 (*m*, H-C(6)); 4.93 (*dd*, *J* = 14.6; 13.3 Hz, CH_2); 7.13–7.32 (*m*, 10H of Arl); 7.39 (*d*, *J* = 9.1 Hz, NH); 7.45–7.54 (*m*, 4H of Arl); 9.94 (*s*, NH). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 32.9, 35.6, 45.8, 55.5, 63.3, 65.0, 115.2, 121.5, 126.1, 127.0, 127.5, 128.1, 128.2, 129.1, 131.7, 137.1, 137.2, 138.7, 146.9, 156.5, 173.9.

***Friedel-Crafts* alkylation of 1-methylindole with *trans*-cinnamaldehyde.** To a solution of catalyst **7** (46 mg, 0.13 mmol) in a mixture of anhydrous CH_2Cl_2 (850 μL) and anhydrous *i*PrOH (150 μL) under Argon at –41 °C was added TFA (10 μL). The solution was stirred for 10 minutes before the addition of *trans*-cinnamaldehyde (190 μL, 1.5 mmol). After stirring for an additional 20 minutes 1-methylindole (64 μL, 0.50 mmol) was added. The resulting mixture was stirred at -41 °C for 48 h. The reaction mixture was transferred into a suspension of $NaBH_4$ (1.5 g) in EtOH (5 mL) and stirred at room temperature. After 1 h the suspension was treated with saturated aqueous $NaHCO_3$ (20 mL), and the mixture was extracted with Et_2O (30 mL). The organic phase was dried over anhydrous Na_2SO_4 and passed through a plug of Silica gel 60 and washed with Et_2O. Volatile components were evaporated *in vacuo* and the residue was used for the determination of conversion (^{1}H-NMR($CDCl_3$)). No reaction took place.

***Michael* addition of dimethyl malonate to *trans*-β-nitrostyrene.** Dimethyl malonate (2.5 mmol, 292 μL) was added to a solution of catalyst **14**, **16**/**16'**, or **18**/**18'** (0.1 mmol, 10 mol%) and *trans*-β-nitrostyrene (149 mg, 1 mmol) in toluene (3 mL) at room temperature and the resulting mixture was stirred for 48 h. The reaction mixture was passed through a plug of Silica gel 60 (EtOAc/petroleum ether = 1:1). Volatile components were evaporated *in vacuo* and the residue was used for the determination of conversion (^{1}H-NMR ($CDCl_3$)). No reaction took place.

Single crystal X-Ray structure analysis for compounds 9 and 18. Single crystal diffraction data for compounds **9** and **18** have been collected on an Agilent SuperNova dual source diffractometer with an Atlas detector at room temperature with Cu Kα (1.54184 Å) and Mo Kα radiation (0.71073 Å), respectively. The data were processed using CrysAlis PRO software.[48] Both structures were solved by direct methods, using SIR97[49]. A full-matrix least-squares refinement on F^2 was employed with anisotropic displacement parameters for all non-hydrogen atoms. H atoms were placed at calculated positions and treated as riding. SHELXL97 software[50] was used for structure refinement and interpretation. Drawings of the structures were produced using ORTEP-3.[51] The agreement factors after final refinement R and wR for compound **18** were very high. Unfortunately we were

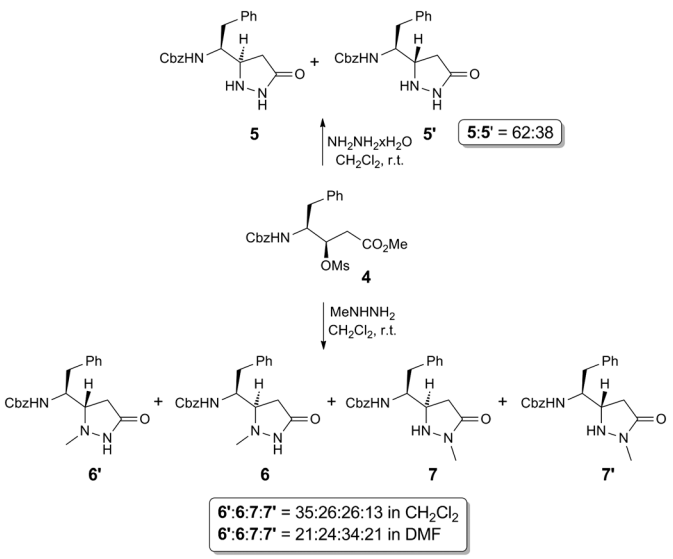


Scheme 2. Synthesis of pyrazolidin-3-one precursor, compound **4**.

not able to get better crystal and collect better diffraction data. Structural and other crystallographic data for compounds **9** and **18** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 917328 and CCDC 921756, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

RESULTS AND DISCUSSION

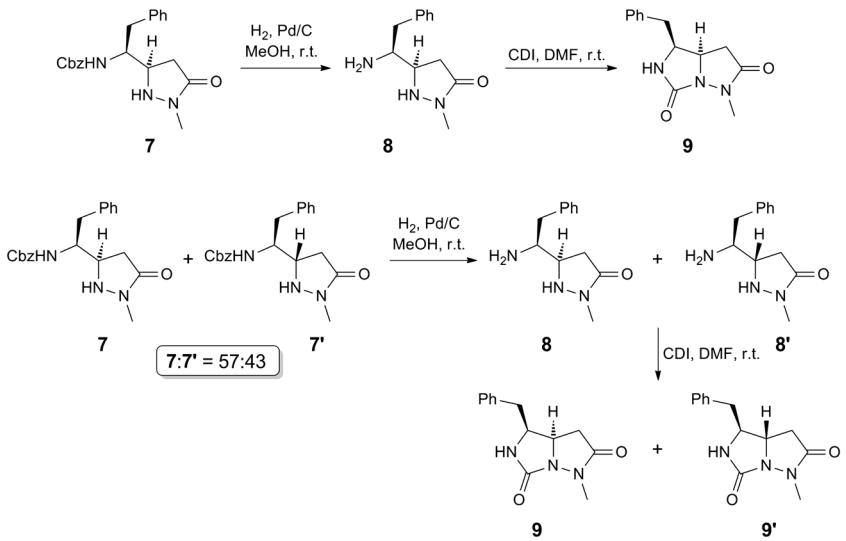
N-Cbz-protected L-phenylalanine **1** was converted into the corresponding *β*-keto ester **2**[46] in 43% yield *via* the addition of Li-enolate of methyl acetate to the reactive imidazolide of **1**. Subsequent reduction of **2** with $NaBH_4$ in MeOH at –5 °C gave a mixture of *β*-hydroxy esters **3** and **3'**[47] in a ratio of **3**:**3'** = 86:14 in 83% yield. Separation by column chromatography or by re-crystallization gave pure diastereomer **3**. Finally, mesylation of **3** in pyridine gave **4** (70% yield), the starting compound for the cyclizations into pyrazolidin-3-ones (Scheme 2).



Scheme 3. Cyclization of mesylate **4** with hydrazine and methylhydrazine.

For the cyclization of mesylate **4**, hydrazine, methylhydrazine, and 1,2-dimethylhydrazine were selected. Reaction of **4** with hydrazine (3 equivalents, r.t.) in methanol proceeded sluggishly with incomplete conversion. Switching the solvent to CH_2Cl_2 and increasing the excess of hydrazine (7 equivalents, r.t., 24 h) yielded the desired pyrazolidin-3-one in full conversion as a mixture of epimers **5**/**5'** in a ratio of **5**:**5'** = 62:38 (crude reaction mixture) and in 57% isolated yields. Increasing the reaction temperature resulted in decreasing yields. All attempts to separate **5**/**5'** failed. Following the same reaction conditions, cyclization of **4** with methylhydrazine yielded two regioizomeric pyrazolidinones each as a mixture of epimers, products **6**/**6'**/**7**/**7'** in a ratio of **6**:**6'**:**7**:**7'** = 35:26:26:13, respectively, and in 100% conversion. Chromatographic separation yielded pure isomers **6**, **6'**, and **7** in 25%, 18%, and 10% yield, respectively. Performing the reaction under identical conditions in DMF did not significantly change the product ratio in the direction of one isomer, furnishing pyrazolidinones **6**/**6'**/**7**/**7'** in a ratio of **6**:**6'**:**7**:**7'** = 21:24:34:21. Reaction of **4** with 1,2-dimethylhydrazine failed to give the expected product (Scheme 3). The poor diastereoselectivity of the formation of **5**/**5'**, **6**/**6'**, and **7**/**7'** implies the substitution of mesylate group with hydrazine proceeded either *via* a mixed S_N1/S_N2 mechanism, or alternatively, under basic conditions, initial elimination of mesylate group takes place, followed by *Michael* addition of hydrazine to *α*,*β*-unsaturated ester with low diastereoselectivity and final cyclization. The formation of two regioisomers in the reaction of **4** with methylhydrazine was not unexpected.

Because, the configuration of the newly created C(5) stereogenic centre in pyrazolidinones **5**-**7**/**5'**-**7'** could not be established using NMR techniques (suitable crystals for single crystal X-ray analysis could not be obtained) was pyrazolidinone **7** first hydrogenated to give Cbz-deprotected diamine **8** followed by cyclization with 1,1'-carbonyldiimidazole (CDI) to give a new bicyclic heterocycle, compound **9**, in



Scheme 4. Synthesis of bicycles **9**/**9'**.

84% yield. Similarly, hydrogenation of a mixture of epimers **7**/**7**' (**7**:**7**' = 57:43) gave an inseparable mixture of amines **8**/**8**', respectively, which were cyclized using CDI into the corresponding and easily separable bicycles **9** and **9**' in 49% and 16% yield, respectively (Scheme 4). The structure of **9** was unambiguously determined by single crystal X-ray analysis (Figure 1). The C(5) stereogenic center forms the tip of the envelope of both pyrazolidinone and imidazolidinone part of the bicyclic system, while the remaining four atoms on each sides of the bicycle lie in their respective planes. In pyrazolidinone part of the molecule, the smaller substituent, H(5), adopts axial position, while in the imidazolidinone part H(5) adopts equatorial position (see the Supporting Information).

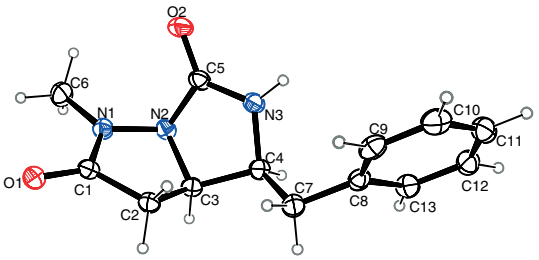
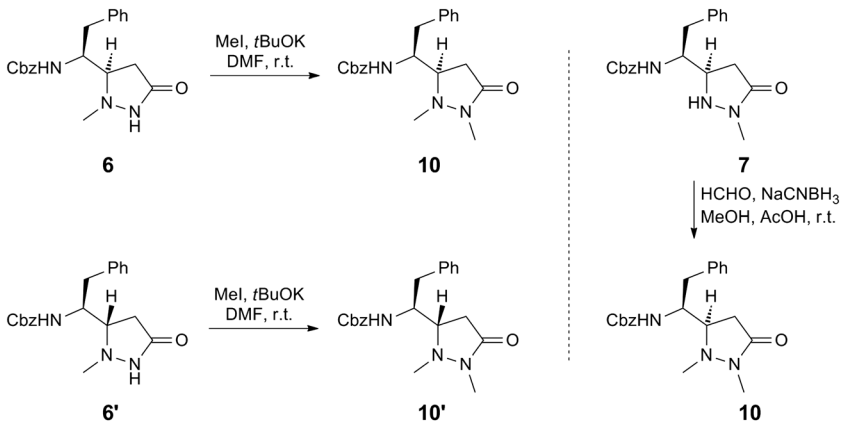


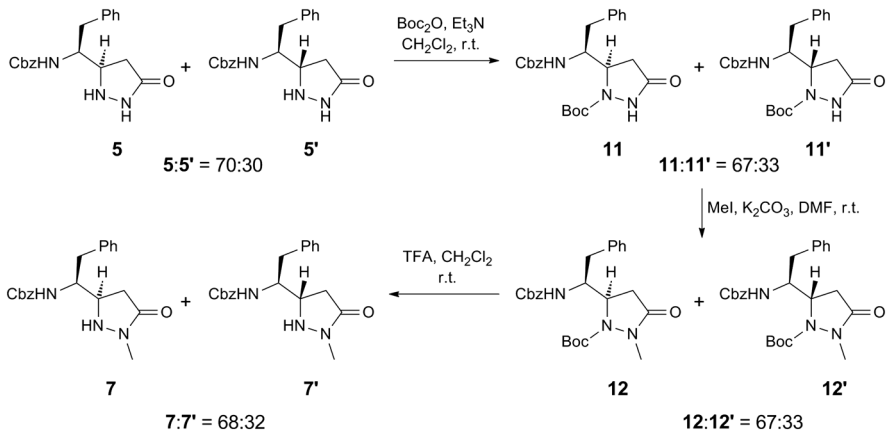
Fig. 1. Single crystal X-ray structure of compound **9**.

Having established the absolute configuration of compound **7** (and therefore also of **7**') the absolute configuration of pyrazolidinones **6**/**6**' was unambiguously determined using chemical correlation with **7**. Compound **7** was reductively methylated using formaldehyde and $NaCNBH_3$ to form 1,2-dimethylpyrazolidinone **10** (41% yield). On the other hand, pyrazolidinones **6** and **6**' were alkylated with iodomethane in the presence of *t*BuOK to form 1,2-dimethylpyrazolidinones **10** and **10**' in 91% and 81% yield, respectively (Scheme 5).

Finally, using chemical correlation with **7**, the absolute configuration of pyrazolidinones **5**/**5**' was determined. Inseparable mixture of epimeres **5**/**5**' (**5**:**5**' = 70:30) were first Boc-protected at N(1) position giving the corresponding products **11**/**11**' in a ratio of **11**:**11**' = 67:33 and 54% yield. Next, the mixture of **11**/**11**' was methylated using MeI in the presence of K_2CO_3 which furnished the corresponding Boc-N(1)-Me-N(2) protected pyrazolidinones **12**/**12**' in a ratio of **12**:**12**' = 67:33 and 97% yield. Deprotection of pyrazolidinones **12**/**12**' with TFA in CH_2Cl_2 gave the corresponding pyrazolidinones **7**/**7**' in a ratio of **7**:**7**' = 68:32 and 66% yield. The relative ratio of the starting pyrazolidinones **5**/**5**' was maintained through the chemical correlation (Scheme 6).



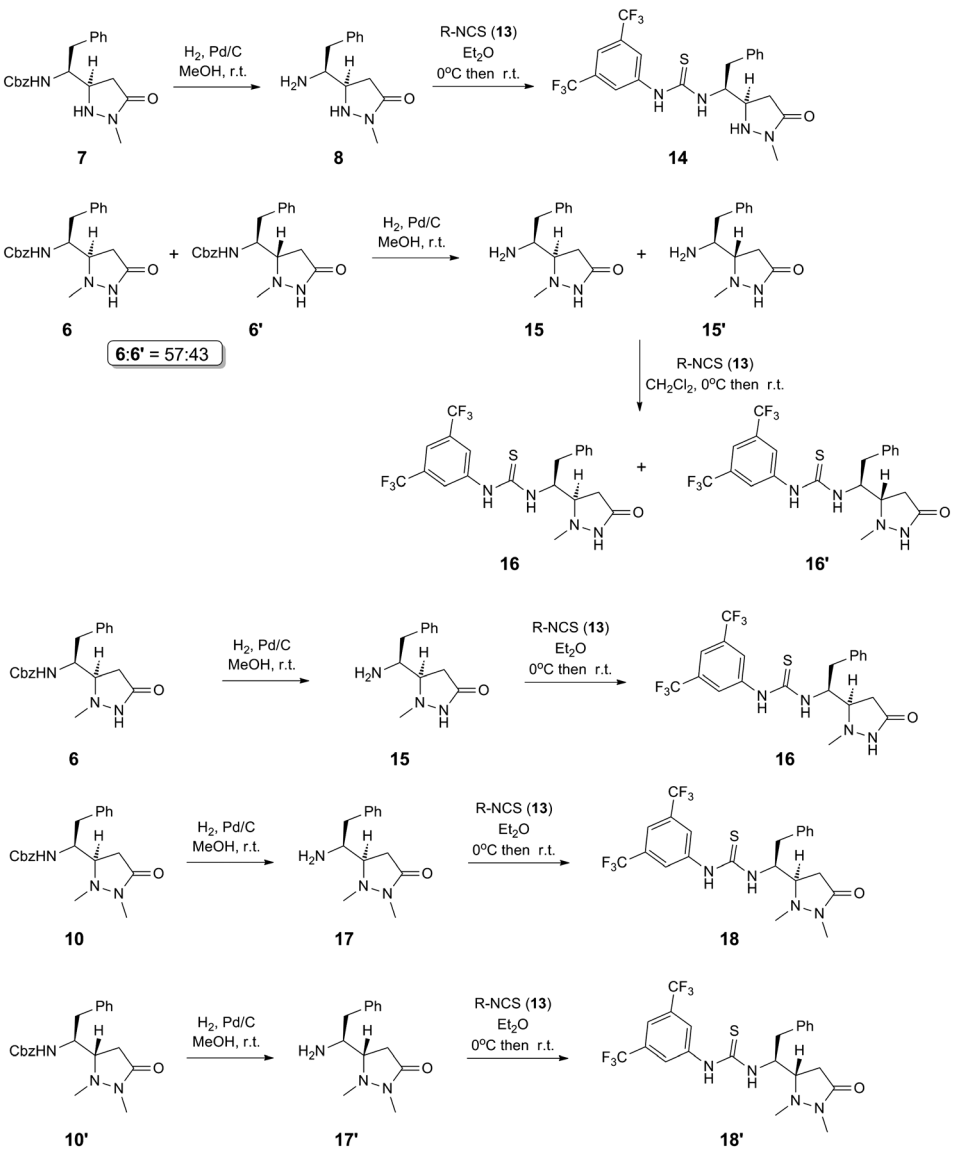
Scheme 5. Chemical correlation of imidazolidinones **6**/**6**' with imidazolidinone **7**.



Scheme 6. Chemical correlation of imidazolidinones **5**/**5**' with imidazolidinone **7**.

Having established the absolute configuration of all the novel pyrazolidinones, a series of (thio)urea derivatives was prepared to check their organocatalytic properties. Diamine **8** (prepared by deprotection of **7**) reacted with 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**13**) selectively with the primary amino group giving thiourea **14** in 64% yield. Similarly, Cbz-deprotection of a mixture of epimers **6**/**6'** (**6**:**6'** = 57:43) gave a mixture of amines **15**/**15'** followed by reaction with isothiocyanate **13** to give after chromatographic separation thioureas **16** and **16'** each in 24% yield, respectively. Alternatively, thiourea **16** was prepared from pure pyrazolidinone **6** *via* Cbz-deprotection into amine **15** and reaction with isothiocyanate **13** in 75% yield. In a similar manner, deprotection of 1,2-dimethylpyrazolidinones **10** and **10'** gave the corresponding amines **17** and **17'**, which were converted with isothiocyanate **13** into thiourea derivatives **18** and **18'** in 59% and 61% yield, respectively (Scheme 7). The structure of **18** was additionally confirmed by single crystal X-ray analysis (Figure 2). As in the structure of compound **9**, C(5) position forms the tip of the envelope, the remaining four atoms of pyrazolidinone ring lying in the plane of the envelope. H(5) adopts equatorial position leaving the large C(5) substituent in the axial position, thus minimizing the strain between the large C(5) substituent and the Me-N(1) substituent[52], the pyramidalization[53] of the N(1) pointing in the direction of the large C(5) substituent (see the Supporting Information).

Further (thio)urea derivatives have been prepared. Thus reaction of amines **15** and **15'**, prepared by catalytic hydrogenation of **6** and **6'**, respectively, with 1-naphthyl isothiocyanate (**19**) gave the corresponding thioureas **20** and **20'** in 49% and 51% yield, respectively. Interestingly, reactions of **15** with more reactive isocyanates, phenyl isocyanate (**21**) and 4-methylphenyl isocyanate (**22**), in slight excess gave bis urea derivatives **23** and **24** in 34% and 44% yield, respectively. Apparently, the hydrazidic N(2) position is nucleophylic enough to react with more electrophilic isocyanates. Reactions with 4-bromophenyl isocyanate (**25**) were repeated with Cbz-protected pyrazolidinones **6** and **6'** giving the expected ureas **26** and **26'** in 63% and 68% yield, respectively (Scheme 8).



Scheme 7. Synthesis of 3,5-bis(trifluoromethyl)phenyl derived thioureas.

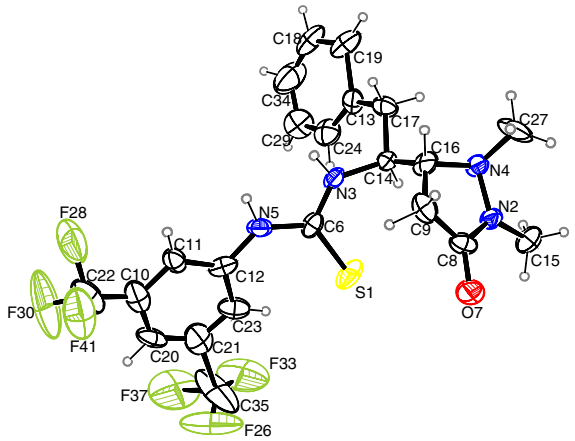
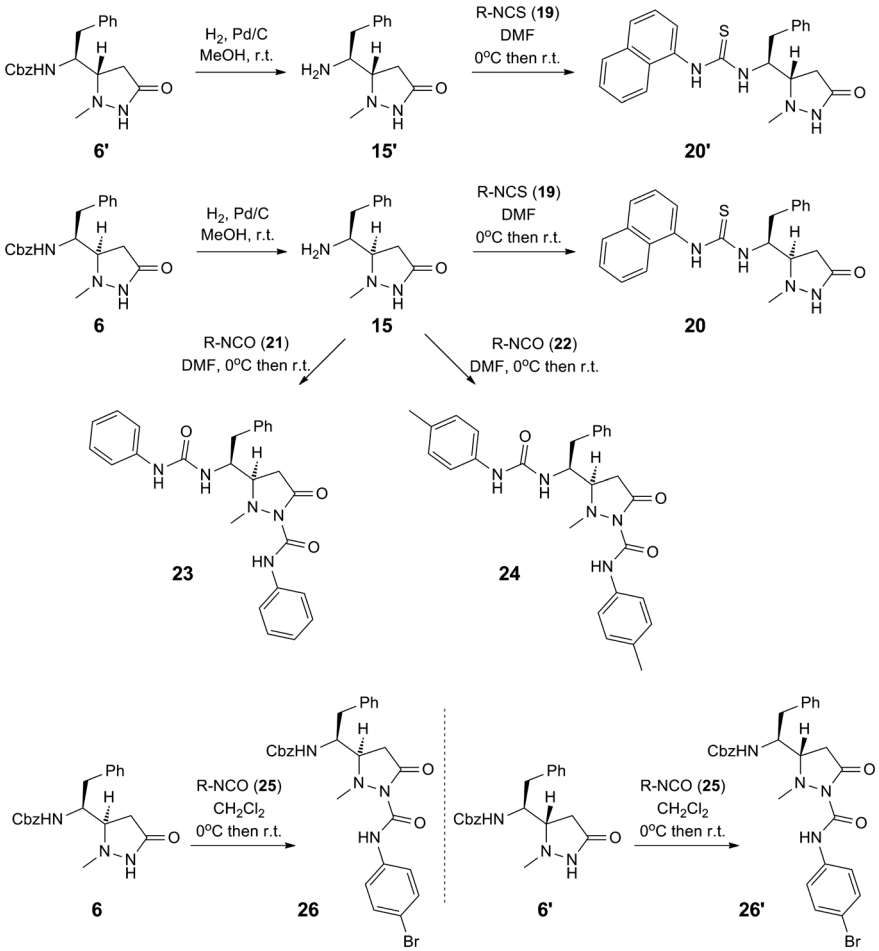


Fig. 2. Single crystal X-ray structure of compound **18**.

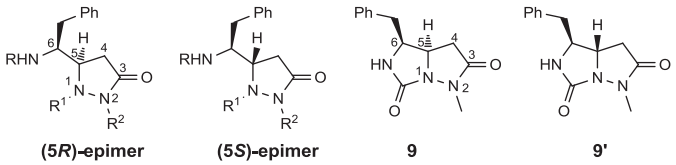
Hoping to find a solid correlation, which would enable a quick assignation of the absolute configuration of the newly formed C(5) stereogenic centre, we looked at proton chemical shifts of pairs of isolated pyrazolidinone epimers, focusing at pyrazolidin-3-one protons and H-C(6) proton (see Table 1). The following trends have been noticed: (i) the H-C(5) and H-C(6) protons of the (5*R*)-epimers **5-7**, **10-12**, **16**, **18**, **20**, **26** are slightly up-field shifted compared to their corresponding (5*S*)-epimers **5'-7'**, **10'-12'**, **16'**, **18'**, **20'**, **26'**; (ii) the H-N(1) and/or H-N(2) protons of (5*S*)-epimers **5'-7'**, **11'** are slightly up-field shifted compared to their (5*R*)-epimer **5-7**, **11** counterparts; (iii) Ha-C(4) and Hb-C(4) proton correlations are not 100% reliable, though in most cases the (5*R*)-epimers have these protons up-field shifted compared to respective (5*S*)-epimers. In the case of bicycles **9**/**9**, the only property standing out is the difference in chemical shift between Ha-C(4) and Hb-C(4) protons *i.e.* for **9** this difference is *ca.* 1 ppm while for **9'** this difference is *ca.* 0.4 ppm. Clearly, the Ha-C(4) proton of **9** must be up field shifted due to the anisotropy caused by the benzyl group in position 6. Furthermore, protons H-C(5) and H-C(6) of **9** appear as multiplets, while in **9'** the corresponding protons appear as a dublet of dublet and as a triplet, respectively. Other properties did not give satisfactory correlations (Table 1).

Finally, selected pyrazolidinones have been tested as potential organocatalysts. First, the cyclic secondary amine **7** has been tested as a potential covalent organocatalyst in the *Friedel-Crasfts* alkylation of 1-methylindole with cinnamaldehyde.[54] Similarly as in recently reported iminium



Scheme 8. Synthesis of (thio)urea derivatives.

TABLE 1. Selected chemical shifts (in ppm) of selected pyrazolidin-3-ones and bicycles 9/9'



Compound	H-N(1)	H-N(2)	Ha-C(4)	Hb-C(4)	H-C(5)	H-C(6)
5	5.45	9.08	2.18	2.37	3.42	3.70
5'	5.28	9.01	2.24	–[a]	3.58	3.80
6	–	9.37	2.13	2.73	2.97	3.65
6'	–	9.32	2.22	2.80	3.11	3.74
7	5.81	–	2.27	2.46	3.36	3.67
7'	5.75		–[a]	–[a]	3.50	3.76
10	–	–	2.19	2.89	2.99	3.60
10'	–	–	2.26	2.96	3.12	3.70
11	–	10.49	2.38	2.88	4.29	3.91
11'	–	10.39	–[a]	2.95	4.45	–[a]
12	–	–	2.36	3.00	4.36	3.81
12'	–	–	–[a]	–[a]	4.47	–[a]
16		–[b]	2.26	2.83	3.18	4.76
16'	–	–[b]	2.24	2.85	3.30	4.78
18[c]	–	–	2.33	2.99	3.27	4.67
18'	–	–	2.36	2.97	3.34	4.82
20	–	–[b]	2.26	2.79	3.13	4.75
20'	–	–[b]	2.30	2.78	3.27	4.81
26	–	–	2.55	3.48	3.20	3.65
26'	–	–	2.67	3.50	3.28	3.81
9[c]	–	–	2.03	3.01	4.21	4.15
9'	–	–	2.32	2.68	4.09	3.80

[a]Overlapped by other signals;
[b]could not be determined unambiguously;
[c]structure determined by single crystal X-ray crystallography.

reactive intermediates derived from imidazolidinone organocatalysts,[54–56] in the hipothetic reactive iminium intermediate derived from **7** and cinnamaldehyde the bulky group in position *5* could serve as the directing group for the attack of the nucleophile (1-methylindole) while the Me group in position *2* would impose the *trans*-configuration around the C=N bond to minimize the nonbonding interactions.[52] Unfortunately, no conversion took place, plausibly due to the choice of the substituent in position *2* and/or too bulky substituent in position *5* (for comparison see Ref. 29) (Figure 3, top).

Next, compounds **14**, **16**, **16' 18**, and **18'** have been tested as potential non-covalent organocatalyst in the *Michael* addition of dimethyl malonate to *trans*-*β*-nitrostyrene.[57] Similarly as *Takemoto's* bifunctional catalyst,[57] where a tertiary amine and thiourea functionalities attached to a chiral scaffold serve to activate both nucleophilic and electrophilic partner in the selected stereoselective transformation, respectively, pyrazolidinones **14**, **16**, **16' 18**, and **18'** poses, similarly, a thiourea and a tertiary or a secondary amine (as part of the cyclic hydrazine derivative) positioned next to each other to catalyze the *Michael* addition. Disappointingly, no reaction took place presumably because of steric/conformational constrains present in our tested catalysts and/or because of the different basicity of our substituted hydrazine part of the catalysts compared to *Takemoto's* tertiary amine part of the catalyst (Figure 3, bottom).

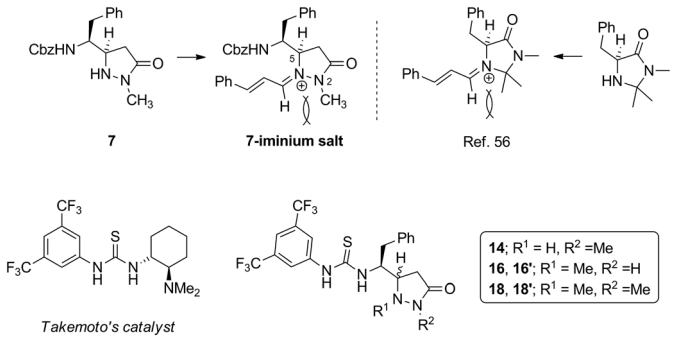


Fig. 3. Selected pyrazolidinones tested as potential organocatalysts.

CONCLUSIONS

In this report, it has been shown, that C(5) substituted pirazolidin-3-ones can be prepared from suitably protected α-amino acid derivatives. In a model reaction, N-Cbz-protected L-phenylalanine was first transformed into the corresponding keto ester, followed by reduction of the keto group, mesylation and cyclization with hydrazine and methylhydrazine. The configurations of the C(5)-epimeric pyrazolidinones were confirmed unambiguously by single crystal X-ray analysis and *via* step by step chemical correlation/interconversion. A series of pyrazolidinone (thio)urea derivatives has been synthesized,

characterized, and eventually tested as potential organocatalysts, although without success. Correlation of proton chemical shifts of pairs of epimeric pirazolidinones suggest that a simple determination of the configuration of the newly created C(5)-stereogenic centre might be possible also for other properly protected α-amino acid derived pyrazolidinones. Additionally, pyrazolidinones derived from α-amino acids could be used to create a library of novel bicyclic derivatives of type **9/9'** or could be selectively derivatized at positions 1, 2, 4 and 6.

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