Resolution of 5-oxo-1-phenylpyrazolidine-3-carboxylic acid and synthesis of novel enantiopure amide derivatives

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Dedicated to Bruce E. Maryanoff and Cynthia A. Maryanoff, in appreciation for their active role in the promotion of chemical science

Abstract
The synthesis is reported of (±)-5-oxo-1-phenylpyrazolidine-3-carboxylic acid, (±)-3, via nucleophilic addition of phenylhydrazine to dimethyl maleate, followed by cyclization of the resulting hydrazine-diestere. The resolution of (±)-3 was achieved via diastereomeric salts employing (R)- and (S)-α-methylbenzylamine as resolving agent. Preferential crystallization of the like (R,R)- and (S,S)- salts allowed the isolation of the desired enantiomerically pure (R)- and (S)- target compounds in up to 87-89 % of the theoretical yield. An X-ray structure of the (S,S)-salt allowed secure assignment of its relative configuration, and thus unequivocal assignment of the absolute configuration in the enantiomeric heterocycles.

Keywords: Resolution, diastereomeric salts, 5-oxo-1-phenylpyrazolidine-3-carboxylic acid, α-methylbenzylamine, chiral amides.

Introduction
5-Oxo-1-arylpazolidines are important heterocycles owing to their potential application as bacterial antibiotics1 or as precursors of carbapenems2 and diazepinones.3 Salient methodologies employed to obtain pyrazolidine derivatives include conjugate addition of hydrazines to α,β-unsaturated imides,4 insertion of diazene derivatives into the cyclopropane ring5 and conjugate addition-rearrangement of hydrazines to α,β-unsaturated sugar δ-lactones.1 However, these methods present some drawbacks, such as low chemoselectivity and enantioselectivity.

In 2006, we reported the preparation of (R)- and (S)-5-oxo-1-phenylpyrazolidine-3-carboxylic acid, (R)- and (S)-3 via resolution with α-methylbenzylamine.6 Soon thereafter, Tzeng
and coworkers independently described the resolution of (±)-3 with L-amino-acid methyl esters.\textsuperscript{7}

We now provide full details of the efficient resolution of 5-oxo-1-phenylpyrazolidine-3-carboxylic acid with α-methylbenzylamine as resolving agent,\textsuperscript{8} as well as the preparation of several enantiopure amide derivatives.

**Results and Discussion**

The racemic dimethyl 2-(2-phenylhydrazinyl)succinate, (±)-2, was prepared from dimethyl maleate 1 by means of nucleophilic addition of phenylhydrazine in methanol at room temperature. Compound (±)-2 was obtained with 89% yield (Scheme 1).\textsuperscript{9}

\[
\begin{align*}
\text{CO}_2\text{CH}_3 + \text{PhNHNNH}_2 & \rightarrow \text{MeOH} \quad \text{r. t., 48 h} \\
& \quad \text{89 %} \\
\text{PhNHNH}_2^+ & \quad \text{MeOH} \\
\text{CO}_2\text{CH}_3 & \quad \text{CO}_2\text{CH}_3 \\
1 & \quad (\pm)-2 \\
\end{align*}
\]

Scheme 1

The hydrazine-diester (±)-2 was treated with sodium methoxide to give the heterocyclic ester (±)-5 in 44% isolated yield (Scheme 2).\textsuperscript{9} The \textsuperscript{1}H- NMR spectrum for heterocycle (±)-5 showed a doublet signal at 5.27 ppm, which was assigned to the exchangeable \(NH\) proton and a doublet of doublet of doublets signal in 4.36 ppm for the tertiary \(CH\) proton. The observed coupling between the proton of the methine group and a \(NH\) proton led to the conclusion that the phenyl substituent must be located at the \(\alpha\)-nitrogen relative to the endocyclic carbonyl group.

\[
\begin{align*}
\text{PhNHNH}_2^+ & \quad \text{CH}_3\text{ONa} \\
\text{CO}_2\text{CH}_3 & \quad \text{MeOH} \\
(\pm)-2 & \quad \text{reflux 3-4 h} \\
& \quad 44 % \\
\text{PhNHNH}_2^+ & \quad \text{MeOH} \\
\text{CO}_2\text{CH}_3 & \quad \text{CO}_2\text{CH}_3 \\
(\pm)-2 & \quad (\pm)-5 \\
\end{align*}
\]

Scheme 2

An X-ray structure of (±)-5, confirmed the conclusions reached from the analysis of the \textsuperscript{1}H-NMR spectra; that is, the phenyl substituent is bound to the \(\alpha\)-nitrogen (Figure 1).
Figure 1. X-ray crystallographic structure of (±)-5 showing the phenyl ring bound to the α-nitrogen.14

The preparation of (±)-5-oxo-1-phenylpyrazolidine-3-carboxylic acid, (±)-3, by direct cyclization of the hydrazine-diester (±)-2 was achieved with potassium carbonate in MeOH-H2O, by heating the reaction mixture under microwave irradiation during 15 minutes, followed by treatment with concentrated HCl.9 The desired product was obtained in 83 % isolated yield (Scheme 3).

Scheme 3.

Enantiomerically pure α-methylbenzylamine has been employed widely as a resolving agent,8,10 thus, the next step consisted in the resolution of (±)-3 via diastereomeric salt formation with this chiral amine. The racemic acid (±)-3 was dissolved in hot ethyl acetate-isopropanol (70:30 v/v) before the addition of half equivalent of (R)- or (S)-α-methylbenzylamine. One diastereomeric salt precipitated from the solution whereas the other one remained in solution. Each diastereomeric salt was obtained in 85 % of the theoretical yield (Scheme 4).

Scheme 4. Resolution of (±)-3 with (R)- and (S)-α-methylbenzylamines.
An X-ray crystallographic structure of the insoluble diastereomeric salt formed with (S)-α-methylbenzylamine allowed for identification of the like\textsuperscript{11} relative configuration, and therefore to the assignment of the (S)- absolute configuration of the stereogenic center of the heterocycle. With this information we determined that precipitation of the like salt is favored (Figure 2).

\textbf{Figure 2.} X-ray crystallographic structure of (S,S)-4 showing the like (S,S) relative configuration of the stereogenic centers.\textsuperscript{14}

The like (R,R)-4 and (S,S)-4 salts were dissolved in aqueous medium and treated with HCl to recover both enantiomers of 3 in free form by filtering the precipitate. Afterward, acids (R)- and (S)-3 were transformed into their corresponding methyl esters through a Fischer’s esterification (Scheme 5). The methyl esters (R)- and (S)-5 were analyzed by chiral HPLC and both showed an enantiomeric excess > 99 \% (see the Experimental Section). Subsequently, protection of the β-nitrogen in enantiomerically pure methyl esters (R)- and (S)-5 was carried out using 4 equivalents of (Boc)\textsubscript{2}O, obtaining (R)- and (S)-6 in good yield. Saponification of N-Boc esters 6 was achieved with lithium hydroxide monohydrate in THF. The expected acids (R)- and (S)-7 were obtained in 83 and 90 \% yields, respectively (Scheme 6).
Scheme 5. Reaction conditions: (a) HCl; (b) H₂SO₄, methanol, MW, reflux, 10 minutes.

The coupling reaction was carried out through the formation of a mixed anhydride with pivaloyl chloride before the addition of the corresponding amine (aniline, benzylamine, (S)-α-methylbenzylamine, or (S)-2-amino-1-butanol) and heating to reflux for 30 minutes. The protected amides 8-11 were obtained with yields from 69 to 88% (Table 1). An X-ray structure was obtained for compound (R,S)-11. Salient observations are the anti-parallel orientation of the carbonyl groups and the lack of hydrogen bonding between the hydroxyl group and the N-H amide function (Figure 3).

Scheme 6. Reaction conditions: (a) Boc₂O, DMAP, Et₃N, CH₂Cl₂, RT, 48 h; (b) LiOH•H₂O, THF, RT, 44 h.
Table 1. Coupling reaction of \((R)-7\) and \((S)-7\) with several amines to afford enantiopure amides \((R)-8-11\) and \((S)-8-11\).

\[
\begin{align*}
1. \text{Cl} & \quad \text{Et}_3\text{N} \\
\text{THF} & \\
2. \text{H}_2\text{N-R} & \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Product</th>
<th>Isolated Yield (%)</th>
<th>Product</th>
<th>Isolated Yield (%)</th>
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<tbody>
<tr>
<td>((R)-8)</td>
<td>83</td>
<td>((S)-8)</td>
<td>88</td>
</tr>
<tr>
<td>((R)-9)</td>
<td>63</td>
<td>((S)-9)</td>
<td>81</td>
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<tr>
<td>((R,S)-10)</td>
<td>79</td>
<td>((S,S)-10)</td>
<td>69</td>
</tr>
<tr>
<td>((R,S)-11)</td>
<td>79</td>
<td>((S,S)-11)</td>
<td>77</td>
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Finally, the N-Boc protecting group was removed with trifluoroacetic acid to obtain the compounds of interest (R)-12-15 and (S)-12-15 in good yields (Table 2). X-ray crystallographic structures were obtained for compounds (S)-12 and (S,S)-15. It can be appreciated in both structures that the carbonyl groups are oriented in parallel (Figure 4).

**Figure 3.** X-ray crystallographic structure of (R,S)-11.

**Figure 4.** X-ray crystallographic structures of (S)-12 (left) and (S,S)-15 (right).
Table 2. Removal of the N-Boc group with trifluoroacetic acid.

An efficient method for the preparation of racemic 5-oxo-1-phenylpyrazolidine-3-carboxylic acid and its subsequent resolution via separation of diastereomeric salts, in three steps with 85% overall yield, has been developed. These chiral acids and several novel amide derivatives reported herein are presently being evaluated as building blocks, ligands, and/or organo-catalysts in asymmetric synthesis.

Conclusions
Experimental Section

**General.** Optical rotations were measured in a Perkin-Elmer 241 polarimeter. Melting points were measured on a Melt-Temp ‘Electrothermal’ apparatus and are uncorrected. NMR spectra were recorded in Bruker Advance 300 (300 MHz) and JOEL Eclipse+400 (400 MHz) spectrometers. IR spectra were recorded on a Perkin-Elmer FTIR spectrum-GX apparatus. Mass spectra were registered on a Hewlett Packard 5989-AMS-ENGINE, Thermo Electron Trace-DSQ spectrometer, at 20 eV. HRMS were recorded on JEOL JMS-SX 102a and Agilent-MSD-TOF1069A spectrometers. Elemental analyses were obtained using a Thermo-Finnigan CHNS/O 1112 apparatus. The structural X-ray crystallographic data were obtained on an Enraf-Nonius Kappa CCD diffractometer. Microwave irradiation was achieved in a single-mode Discover System reactor from CEM Corporation. HPLC analyses were carried out with a Waters 600 E equipment fitted with a UV/Visible Waters 2487 detector at 230 nm and Chiralpack AD (Daicel Chemical Ind., LTD, 0.46 x 25 cm) column, employing hexane-PrOH (90:10) as mobile phase, and 1 mL/min flow.

**Dimethyl maleate 1.** In a 500 mL three-necked round-bottomed flask equipped with a magnetic stirrer and a reflux condenser, 35 g (301.7 mmol) of maleic acid were placed and dissolved with 200 mL of methanol before the addition of 3.5 g (18.4 mmol, 10 w/w %) of p-toluenesulfonic acid and the flask was heated to reflux for 11 h. After this time, the solvent was concentrated under vacuum and the crude reaction mixture was treated with a saturated solution of NaHCO₃ (100 mL) and extracted with ethyl acetate (3x30 mL). The organic layer was dried with anhydrous Na₂SO₄ and concentrated under vacuum to provide 1 (36.2 g, 84 % yield) as a colorless oil. $^1$H- NMR (CDCl₃, 270 MHz): $\delta = 6.22$ (s, 2H, $HC=CH$), 3.77 (s, 6H, OCH₃). $^{13}$C-NMR (CDCl₃, 67.9 MHz): $\delta = 165.7$ (C=O), 129.8 (C=C), 52.2 (OCH₃).

**(±)**-Dimethyl 2-(2-phenylhydrazinyl)succinate, (±)-2. In a 250 mL round-bottomed flask equipped with a magnetic stirrer and an addition funnel, 8.4 g (58.33 mmol) of dimethyl maleate 1 were placed and dissolved in 80 mL of methanol under nitrogen atmosphere. Subsequently, 4.8 mL (46.61 mmol, 5.25 g) of phenylhydrazine was added slowly and the reaction mixture was stirred during 48 h at room temperature. After this time, approximately one third of the solvent was evaporated under vacuum and the flask was cooled to 0 °C, observing a precipitate which corresponded to dimethyl fumarate (1.15 g), $^{12}$ which was filtered off, and washed twice with cold methanol (15 mL). The filtrate was evaporated under vacuum to provide a solid, which was suspended in hexane (15 mL) and filtered affording 10.5 g of (±)-2 (89% yield) as a yellow solid, mp 44-46 °C. $^1$H- NMR (CDCl₃, 400 MHz): $\delta = 2.82$ (dd, $J = 6.9, 16.4$ Hz, 1H, CH₂), 2.87 (dd, $J = 5.1, 16.3$ Hz, 1H, CH₂), 3.71 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 3.95 (dd, $J = 5.3, 6.6$ Hz, 1H, CH), 4.41 (br, 1H, NH), 5.74 (br, 1H, NH), 6.76-6.82 (m, 1H, ArCH), 6.84-6.91 (m, 2H, ArCH), 7.16-7.23 (m, 2H, ArCH). $^{13}$C- NMR (CDCl₃, 100.5 MHz): $\delta = 35.6$ (CH₂), 52.0 (OCH₃), 52.5 (OCH₃), 59.2 (CH), 113.1 (2xArCH), 119.4 (ArCH), 129.1 (2xArCH), 149.0 (Cipso), 171.5 (C=O), 173.7 (C=O). MS (IE) $m/z$ (%): 252 (M⁺, 88), 193 (46), 161 (37), 133 (15), 119 (70); 107
(100), 92 (99), 77 (67), 65 (63). IR νmax (KBr) cm⁻¹: 3324, 2954, 1739, 1630, 1603, 1437, 1220, 996, 754. Anal. Calcd. for C₁₂H₁₆N₂O₄ (252.27): C 57.13, H 6.39, N 11.10; Found: C 57.42, H 6.31, N 11.18%.

(±)-5-Oxo-1-phenylpyrazolidine-3-carboxylic acid (±-3). In a 100 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser, 3.12 g (12.3 mmol) of (±)-2 was placed and dissolved in 30 mL of methanol before the addition of 1.7 g (12.3 mmol) of K₂CO₃ dissolved in 18 mL of water. The reaction mixture was set in the microwave equipment and maintained at reflux for 15 min with 75 Watts of power. The methanol solvent was evaporated and 50 mL of water was added before addition of concentrated HCl to acidify until pH 2.0, at which point the desired product precipitated. The solid was filtered off, washed with water and dried under vacuum at 40 °C during 48 h. It was then recrystallized twice from hot methanol and dried under vacuum 18 mL of water. The reaction mixture was set in the microwave equipment and maintained at reflux for 15 min with 75 Watts of power. The methanol solvent was evaporated and 50 mL of water was added before addition of concentrated HCl to acidify until pH 2.0, at which point the desired product precipitated. The solid was filtered off, washed with water and dried under vacuum at 40 °C during 48 h. It was then recrystallized twice from hot methanol and dried under vacuum to give the product (±)-3 (2.1 g, 83 % yield) as a white powder, mp 210-212 °C [Lit.¹³ mp 197-199 °C]. ¹H- NMR (DMSO-d₆, 400 MHz): δ = 2.76 (dd, J = 5.9, 16.5 Hz, 1H, CH₂), 2.98 (dd, J = 8.6, 16.5 Hz, 1H, CH₂), 4.24 (dd, J = 5.9, 8.1 Hz, 1H, CH₂), 6.55 (br, 1H, NH), 7.05-7.11 (m, 1H, ArCH), 7.31-7.39 (m, 2H, ArCH), 7.75-7.82 (m, 2H, ArCH), 13.0 (br, 1H, CO₂H). ¹³C- NMR (DMSO-d₆, 100.5 MHz): δ = 37.8 (CH₂), 55.4 (CH), 118.4 (2xArCH), 124.1 (ArCH), 129.0 (2xArCH), 139.5 (Cipso), 170.6 (NC=O), 172.9 (CO₂H). MS (IE) m/z (%): 206 (M⁺, 100), 161 (55), 118 (13), 107 (35), 91 (17), 77 (20), 55 (5).

(R)-1-Phenylethylammonium (R)-5-oxo-1-phenylpyrazolidine-3-carboxylate, (R,R-4). In a 1 L three-necked round-bottomed flask equipped with a magnetic stirrer, an addition funnel and a reflux condenser, 10.5 g (50.9 mmol) of (±)-3 was dissolved in 570 mL of EtOAc-i-PrOH (70:30, v/v) and the resulting mixture was heated until the solution became homogeneous. Subsequently, 3.1 g (25.45 mmol, 3.24 mL) of (R)-α-methylbenzylamine was added and the reaction mixture was heated to reflux for 15 min, at which point the expected like salt precipitates (see main text). The heating was stopped and the mixture stirred until it reached room temperature. The reaction mixture was then cooled in an ice-bath for 30 min and the precipitate filtered, washed with 30 mL of EtOAc, and dried under vacuum at 40 °C during 24 h to obtain 7.0 g of (R,R)-4 (85 % yield) as a white solid, mp 190-192 °C, [α]D²⁰ = + 63.0 (c 2, MeOH). ¹H- NMR (DMSO-d₆, 400 MHz): δ = 1.48 (d, J = 6.8 Hz, 3H, CH₃), 2.70 (dd, J = 9.4, 16.6 Hz, 1H, CH₂), 2.75 (dd, J = 8.8, 16.7 Hz, 1H, CH₂), 3.82 (dd, J = 8.8, 9.2 Hz, 1H, *CH), 4.33 (q, J = 6.7 Hz, 1H, *CH), 7.04-7.08 (m, 1H, ArCH), 7.29-7.39 (m, 5H, ArCH), 7.47-7.51 (m, 2H, ArCH), 7.78-7.81 (m, 2H, ArCH). ¹³C- NMR (DMSO-d₆, 100.5 MHz): δ = 21.9 (CH₃), 39.1 (CH₂), 50.4 (*CH), 57.4 (*CH), 118.2 (2xArCH), 123.8 (ArCH), 127.2 (2xArCH), 128.6 (ArCH), 129.0 (2xArCH), 129.1 (2xArCH), 139.7 (Cipso), 141.2 (Cipso), 170.9 (NC=O), 173.8 (OC=O). MS (IE) m/z (%): 206 (M⁺–121, 100), 161 (64), 119 (12), 107 (41) 77 (18), 43 (3). Anal. Calcd. for C₁₇H₁₇N₃O₃ (327.38): C 66.04, H 6.47, N 12.84; Found: C 66.28, H 6.60, N 12.88%.

(S)-1-Phenylethylammonium (S)-5-oxo-1-phenylpyrazolidine-3-carboxylate, (S,S-4). The same procedure described above was followed to afford 7.0 g (85 % yield) of the desired salt (S,S)-4 as a white solid, mp 188-190 °C, [α]D²⁰ = – 64.2 (c 2, MeOH). ¹H- NMR (DMSO-d₆, 400 MHz): δ
= 1.47 (d, J = 6.8 Hz, 3H, CH₃), 2.70 (dd, J = 9.4, 16.5 Hz, 1H, CH₂), 2.75 (dd, J = 8.7, 16.6 Hz, 1H, CH₂), 3.82 (dd, J = 9.0, 9.2 Hz, 1H, *CH), 4.34 (q, J = 6.8 Hz, 1H, *CH), 7.03-7.08 (m, 1H, ArCH), 7.30-7.39 (m, 5H, ArCH), 7.47-7.49 (m, 2H, ArCH), 7.79-7.81 (m, 2H, ArCH). ¹³C-NMR (DMSO-d₆, 100.5 MHz): δ = 21.9 (CH₃), 39.1 (CH₂), 50.4 (*CH), 57.4 (*CH), 118.2 (2xArCH), 123.8 (ArCH), 127.2 (2xArCH), 128.5 (ArCH), 129.0 (2xArCH), 129.1 (2xArCH), 130.0 (3.9 g, 89% yield) was obtained as a white solid, mp 208-210 °C, [α]D²⁰ = + 60.8 (c 1, MeOH). ¹H- NMR (DMSO-d₆, 400 MHz): δ = 2.76 (dd, J = 5.9, 16.1 Hz, 1H, CH₂), 2.98 (dd, J = 8.6, 16.4 Hz, 1H, CH₂), 4.23 (dd, J = 6.1, 8.1 Hz, 1H, *CH), 6.55 (br, 1H, NH), 7.06-7.11 (m, 1H, ArCH), 7.32-7.37 (m, 2H, ArCH), 7.76-7.79 (m, 2H, ArCH), 13.0 (br, 1H, CO₂H). ¹³C-NMR (DMSO-d₆, 100.5 MHz): δ = 37.8 (CH₃), 55.4 (*CH), 118.4 (2xArCH), 124.1 (ArCH), 129.0 (2xArCH), 139.6 (Cipso), 170.6 (NC=O), 172.8 (CO₂H). MS (IE) m/z (%): 206 (M⁺ – 121, 100), 161 (74), 119 (18), 107 (62), 91 (24), 77 (29), 44 (14). Anal. Calcd. for C₁₅H₁₂N₂O₃: C 66.04, H 6.47, N 12.84; Found: C 66.34, H 6.23, N 12.96%.

(R)-5-OxO-1-phenylpyrazolidine-3-carboxylic acid, (R-3). In a 500 mL Erlenmeyer flask provided with a magnetic stirrer, 7.0 g (21.4 mmol) of salt (R,R)-4 was dissolved in 200 mL of water. The pH was adjusted to 2.0 with 7 mL of conc. HCl, the solution was placed in an ice-bath, and was stirred until precipitation of the acid. The precipitate was filtered off, washed with water and dried under vacuum at 40 °C during 48 h. The desired product (R-3) (3.9 g, 89% yield) was obtained as a white solid, mp 208-210 °C, [α]D²⁰ = + 60.8 (c 1, MeOH). ¹H- NMR (DMSO-d₆, 400 MHz): δ = 2.76 (dd, J = 5.9, 16.1 Hz, 1H, CH₂), 2.98 (dd, J = 8.6, 16.4 Hz, 1H, CH₂), 4.23 (dd, J = 6.1, 8.1 Hz, 1H, *CH), 6.55 (br, 1H, NH), 7.06-7.11 (m, 1H, ArCH), 7.32-7.37 (m, 2H, ArCH), 7.76-7.79 (m, 2H, ArCH), 13.0 (br, 1H, CO₂H). ¹³C-NMR (DMSO-d₆, 100.5 MHz): δ = 37.8 (CH₃), 55.4 (*CH), 118.4 (2xArCH), 124.1 (ArCH), 129.0 (2xArCH), 139.6 (Cipso), 170.6 (NC=O), 172.8 (CO₂H). MS (IE) m/z (%): 206 (M⁺, 100), 161 (56), 118 (14), 107 (61), 93 (20), 77 (19), 55 (5). IR νmax (KBr) cm⁻¹: 3442, 3231, 2538, 1730, 1650, 1592, 1488, 1374, 1224, 1008, 763. Anal. Calcd. for C₁₅H₁₂N₂O₃: C 58.25, H 4.89, N 13.59; Found: C 58.39, H 5.29, N 13.69%.

(S)-5-OxO-1-phenylpyrazolidine-3-carboxylic acid, (S-3). The procedure described above (using the same quantities of reagents) was followed to afford the enantiopure carboxylic acid (S)-3 (3.8 g, 87% yield) as a white solid, mp 212-214 °C, [α]D²⁰ = – 59.6 (c 1, MeOH). ¹H- NMR (DMSO-d₆, 400 MHz): δ = 2.75 (dd, J = 5.9, 16.6 Hz, 1H, CH₂), 2.98 (dd, J = 8.6, 16.4 Hz, 1H, CH₂), 4.24 (dd, J = 6.1, 8.6 Hz, 1H, *CH), 6.54 (br, 1H, NH), 7.05-7.12 (m, 1H, ArCH), 7.32-7.38 (m, 2H, ArCH), 7.76-7.80 (m, 2H, ArCH), 13.0 (br, 1H, CO₂H). ¹³C-NMR (DMSO-d₆, 100.5 MHz): δ = 37.8 (CH₃), 55.4 (*CH), 118.4 (2xArCH), 124.1 (ArCH), 129.0 (2xArCH), 139.6 (Cipso), 170.6 (NC=O), 172.8 (CO₂H). MS (IE) m/z (%): 206 (M⁺, 100), 161 (69), 118 (19), 107 (56), 93 (22), 77 (24), 55 (6). IR νmax (KBr) cm⁻¹: 3454, 3209, 2554, 1740, 1690, 1593, 1494, 1355, 1206, 1018, 753.

(R)-Methyl 5-oxo-1-phenylpyrazolidine-3-carboxylate, (R-5). In a 100 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser, were added 5.0 g (24.3 mmol) of (R)-3, 80 mL of methanol, and a catalytic amount of sulfuric acid. The reaction mixture was placed in the microwave equipment and was heated to reflux during 10 min using a power of 50 Watts. The reaction mixture was then concentrated in the rotary evaporator and allowed to cool to RT before the addition of 25 mL of water. The pH of the aqueous solution was adjusted to 8.0 by addition of aqueous NaHCO₃ to subsequently extract (3x25 mL) the organic product with ethyl acetate. The organic phase was washed with brine, dried with anhyd. Na₂SO₄ and
concentrated. The concentrate was recrystallised from 7 mL of hexane-EtOAc (8:2 v/v) to give 5.1 g (96 % yield) of product (R)-5 as a white solid, mp 100-102 °C, [α]D20 = +88.2 (c 1, CHCl3), >99 % ee. 1H- NMR (CDCl3, 400 MHz): δ = 2.95 (dd, J = 9.3, 16.7 Hz, 1H, CH2), 3.00 (dd, 1H, J = 8.8, 16.8 Hz), 3.82 (s, 3H, CH3), 4.35 (ddd, J = 8.8, 9.2, 9.5 Hz, 1H, *CH), 5.27 (d, J = 9.5 Hz, 1H, NH), 7.11-716 (m, 1H, ArCH), 7.32-7.39 (m, 2H, ArCH). 13C- NMR (CDCl3, 100.5 MHz): δ = 37.9 (CH2), 52.9 (CH3), 55.4 (*CH), 118.6 (2xArCH), 124.7 (ArCH), 128.8 (2xArCH), 138.3 (Cipso), 168.3 (NC=O), 171.3 (OC=O). MS (IE) m/z (%): 220 (M++, 100), 178 (4), 161 (62), 118 (6), 107 (8), 91 (2). IR νmax (KBr) cm−1: 3446, 3216, 2332, 1742, 1594, 1494, 1243, 1032, 768. The enantiomeric excess was determined by HPLC using a chiral Chiralpak AD column, 230 nm, mobile phase hexane-i-PrOH (90:10), and flow 1 mL/min. Retention time: 27.08 min (R).

(S)-Methyl 5-oxo-1-phenylpyrazolidine-3-carboxylate, (S-5). The procedure described above was followed to produce the desired ester (S)-5, employing 4.6 g (22.4 mmol) of (S)-3, 75 mL of methanol and a catalytic amount of sulfuric acid. 4.77 g of (S)-5 were obtained (97% yield), as a white solid, mp 100-102 °C, [α]D20 = −89.0 (c 1, CHCl3), >99 % ee. 1H- NMR (CDCl3, 400 MHz): δ = 2.94 (dd, J = 9.3, 16.7 Hz, 1H, CH2), 2.99 (dd, J = 8.8, 16.5 Hz, 1H, CH2), 3.83 (s, 3H, CH3), 4.36 (ddd, J = 8.8, 9.2, 9.5 Hz, 1H, *CH), 5.27 (d, J = 9.9 Hz, 1H, NH), 7.10-7.16 (m, 1H, ArCH), 7.32-7.39 (m, 2H, ArCH), 7.79-7.85 (m, 2H, ArCH). 13C- NMR (CDCl3, 100.5 MHz): δ = 38.0 (CH2), 53.0 (CH3), 55.4 (*CH), 118.6 (2xArCH), 124.8 (ArCH), 128.9 (2xArCH), 138.3 (Cipso), 168.4 (NC=O), 171.3 (OC=O). MS (IE) m/z (%): 220 (M++, 100), 178 (4), 161 (86), 119 (6), 107 (9), 91 (2). IR νmax (KBr) cm−1: 3458, 3216, 2379, 1742, 1594, 1592, 1495, 1241, 1032, 766. Anal. Calcd. for C11H12N2O3 (220.22): C 59.99, H 5.49, N 12.72; Found: C 60.17, H 5.80, N 12.77%. The enantiomeric excess was determined by HPLC using a chiral Chiralpak AD column, 230 nm, mobile phase hexane-i-PrOH (90:10), and flow 1 mL/min. Retention time: 18.95 min (S).

(R)-1-tert-Butyl 5-methyl 3-oxo-2-phenylpyrazolidine-1,5-dicarboxylate, (R-6). In a 250 mL round-bottomed flask equipped with a magnetic stirrer were placed 4.5 g (20.4 mmol) of (R)-5, 5.0 g (40.9 mmol) of DMAP and 4.2 g (40.9 mmol, 5.7 mL) of Et3N. These reagents were dissolved in 100 mL of CH2Cl2 and the resulting mixture was stirred during 10 minutes before the addition of 4.5 g (1 equiv., 20.4 mmol) of (Boc)2O. Three additional equivalents of (Boc)2O were added to the solution - one equivalent each three hours to complete a total of 18.0 g (81.7 mmol) of (Boc)2O. The reaction mixture was stirred for 39 additional hours after the addition of the fourth equivalent. The solution was extracted three times with 50 mL of CH2Cl2 and 50 mL of water, adjusting the pH to 4 and washing the organic phase with brine. The organic phase was dried with anhyd. Na2SO4 and then the CH2Cl2 solvent was evaporated under vacuum. The crude product was purified by column chromatography (hexane-EtOAc, 85:15 v/v) and recrystallised from hexane-EtOAc (7:3 v/v), obtaining 5.4 g (83% yield) of (R)-6 as a white solid, mp 98-100 °C, [α]D20 = +61.4 (c 1, CHCl3). 1H- NMR (CDCl3, 400 MHz): δ = 1.27 (s, 9H, C(CH3)3), 2.87 (dd, J = 1.1, 17.2 Hz, 1H, CH2), 3.29 (dd, J = 9.9, 17.2 Hz, 1H, CH2), 3.81 (s, 3H, CH3), 5.22 (dd, J = 1.1, 9.9 Hz, 1H, *CH), 7.14-7.20 (m, 1H, ArCH), 7.34-7.40 (m, 2H, ArCH),
7.57-7.62 (m, 2H, ArCH). $^{13}$C- NMR (CDCl$_3$, 100.5 MHz): $\delta$ = 27.8 (C(CH$_3$_3)), 35.6 (CH$_2$), 53.0 (CH$_3$), 58.1 (*CH), 83.9 (C(CH$_3$_3)), 120.4 (2xArCH), 125.5 (ArCH), 128.6 (2xArCH), 138.9 (C$_{ipso}$), 155.3 (OC=ON), 167.7 (NC=O), 170.1 (OC=O). MS (IE) m/z (%): 320 (M$^+$, 3), 220 (100), 161 (60), 118 (3), 107 (4), 57 (30). IR $\nu_{\max}$ (KBr) cm$^{-1}$: 3426, 2980, 2345, 1762, 1741, 1736, 1594, 1310, 1152, 1022, 757.

(S)-1-tert-Butyl 5-methyl 3-oxo-2-phenylpyrazolidine-1,5-dicarboxylate, (S-6). The procedure described above was followed to obtain the N-Boc protected ester (S-6), employing 3.6 g (16.36 mmol) of (S)-5, 4.0 g (32.7 mmol) of DMAP, 80 mL of CH$_2$Cl$_2$, 3.3 g (32.7 mmol, 4.6 mL) of Et$_3$N and 14.4 g (65.4 mmol) of (Boc)$_2$O. The desired product 4.5 g (6.8% yield) was obtained as a white solid, mp 98-100 °C, $[\alpha]_D^{20} = -62.1$ (c 1, CHCl$_3$). $^1$H- NMR (CDCl$_3$, 400 MHz): $\delta$ = 1.26 (s, 9H, C(CH$_3$_3)), 2.87 (dd, $J$ = 1.3, 17.0 Hz, 1H, CH$_2$), 3.30 (dd, $J$ = 9.7, 17.0 Hz, 1H, CH$_2$), 3.80 (s, 3H, CH$_3$), 5.22 (dd, $J$ = 1.1, 9.5 Hz, 1H, *CH), 7.14-7.20 (m, 1H, ArCH), 7.34-7.39 (m, 2H, ArCH), 7.57-7.62 (m, 2H, ArCH). $^{13}$C- NMR (CDCl$_3$, 100.5 MHz): $\delta$ = 27.8 (C(CH$_3$_3)), 35.6 (CH$_2$), 53.0 (CH$_3$), 58.1 (*CH), 83.9 (C(CH$_3$_3)), 120.4 (2xArCH), 125.5 (ArCH), 128.6 (2xArCH), 138.9 (C$_{ipso}$), 155.3 (OC=ON), 167.7 (NC=O), 170.2 (OC=O). MS (IE) m/z (%): 320 (M$^+$, 8), 220 (100), 161 (59), 118 (4), 107 (5), 77 (3), 57 (27). IR $\nu_{\max}$ (KBr) cm$^{-1}$: 3426, 2980, 2345, 1762, 1741, 1736, 1594, 1310, 1152, 1022, 757. Anal. Calcd. for C$_{16}$H$_{20}$N$_2$O$_5$ (320.34): C 59.99, H 6.29, N 8.74; Found: C 60.37, H 6.69, N 8.75%.

(R)-2-(tert-Butoxycarbonyl)-5-oxo-1-phenylpyrazolidine-3-carboxylic acid, (R-7). In a 500 mL round-bottomed flask equipped with a magnetic stirrer were placed 5.27 g (16.45 mmol) of (R)-6, 100 mL of THF and 1.03 g (24.7 mmol) of LiOH•H$_2$O and the reaction mixture was stirred during 44 h at room temperature. The solvent was evaporated and 50 mL of EtOAc was added before extracting with 100 mL of a saturated aqueous solution of NaHCO$_3$. The organic phase was extracted again with 90 mL of water. The pH of the aqueous phase was adjusted to 3.0 with a saturated solution of tartaric acid and extracted five times with 50 mL of EtOAc and the organic phase was washed with brine, dried with anhyd. Na$_2$SO$_4$ and concentrated under vacuum. The crude product was purified by column chromatography (CHCl$_3$-MeOH, 95:5 v/v) to afford 4.51 g (90% yield) of (R)-7 as a white solid, mp 138-140 °C, $[\alpha]_D^{20} = +49.9$ (c 1, CHCl$_3$). $^1$H- NMR (DMSO-$d_6$, 400 MHz, 120 °C): $\delta$ = 1.30 (s, 9H, C(CH$_3$_3)), 2.67 (dd, $J$ = 1.3, 17.0 Hz, 1H, CH$_2$), 3.37 (dd, $J$ = 9.3, 17.0 Hz, 1H, CH$_2$), 5.05 (dd, $J$ = 1.2, 9.6 Hz, 1H, *CH), 7.12-7.18 (m, 1H, ArCH), 7.32-7.39 (m, 2H, ArCH), 7.50-7.56 (m, 2H, ArCH). $^{13}$C- NMR (DMSO-$d_6$, 100.5 MHz, 120 °C): $\delta$ = 28.2 (C(CH$_3$_3)), 35.8 (CH$_2$), 59.3 (*CH), 83.2 (C(CH$_3$_3)), 120.8 (2xArCH), 125.3 (ArCH), 128.7 (2xArCH), 140.0 (C$_{ipso}$), 155.5 (OC=ON), 169.5 (NC=O), 171.7 (CO$_2$H). MS (IE) m/z (%): 306 (M$^+$, 2), 206 (47), 161 (35), 107 (11), 77 (8), 37 (100), 41 (17). IR $\nu_{\max}$ (KBr) cm$^{-1}$: 3440, 2980, 2624, 1742, 1728, 1598, 1317, 1156, 753. HRMS (ESI-TOF) calculated for C$_{13}$H$_{18}$N$_2$O$_3$ + H$^+$: 307.1288; Found: 307.1288.

(S)-2-(tert-Butoxycarbonyl)-5-oxo-1-phenylpyrazolidine-3-carboxylic acid, (S-7). The procedure described above was followed with 4.87 g (15.21 mmol) of (S)-6, 100 mL of THF and 0.96 g (22.8 mmol) of LiOH•H$_2$O to afford the desired N-Boc protected carboxylic acid (S)-7 in 89 % yield (4.15 g) as a white solid, mp 136-138 °C, $[\alpha]_D^{20} = -50.1$ (c 1, CHCl$_3$). $^1$H- NMR
(DMSO-\(d_6\), 400 MHz, 120 °C): \(\delta = 1.30\) (s, 9H, C(CH\(_3\))\(_3\)), 2.68 (dd, \(J = 1.4\), 17.0 Hz, 1H, CH\(_2\)), 3.39 (dd, \(J = 9.4\), 16.9 Hz, 1H, CH\(_2\)), 5.07 (dd, \(J = 1.5\), 9.4 Hz, 1H, *CH), 7.13-7.19 (m, 1H, ArCH\(_H\)), 7.30-7.39 (m, 2H, ArCH\(_H\)), 7.48-7.55 (m, 2H, ArCH\(_H\)). \(^{13}\)C-\(\text{NMR}\) (DMSO-\(d_6\), 100.5 MHz, 120 °C): \(\delta = 28.1\) (C(CH\(_3\))\(_3\)), 35.7 (CH\(_2\)), 59.1 (*CH), 83.3 (C(CH\(_3\))\(_3\)), 121.0 (2xArCH), 125.3 (ArCH), 128.8 (2xArCH), 139.9 (C\(_{ipso}\)), 155.5 (OC=ON), 169.4 (NC=O), 171.5 (CO3H). MS (IE) \(m/z\) (%): 306 (M\(^+\), 1), 206 (43), 161 (32), 107 (12), 77 (8), 57 (100). IR \(\nu_{\text{max}}\) (KBr) cm\(^{-1}\): 3446, 2980, 2624, 1742, 1728, 1598, 1317, 1156, 748.

**General procedure for the preparation of amides 8-11**

The required quantity of the corresponding precursor, the N-Boc protected carboxylic acid was dissolved with dry THF in a round-bottomed flask equipped with a magnetic stirrer and an addition funnel. An equimolar amount of Et\(_3\)N was added to the solution and the resulting mixture was stirred for ten minutes. At this moment, the flask was placed in an ice-bath and one equivalent of pivaloyl chloride was added slowly during approximately ten minutes. The reaction mixture was stirred at 0 °C during 1 h, and then one equivalent of the corresponding amine was added. The flask was subsequently set inside the microwave equipment and the reaction mixture was heated at 70 °C during 30 minutes, using a power of 75 Watts. Afterwards, the solvent was evaporated and the crude product was extracted with EtOAc, the organic phase was washed with brine, dried with Na\(_2\)SO\(_4\) and concentrated under vacuum. The product was recrystallised from hexane-EtOAc (9:1 v/v), filtered and dried at 40 °C under vacuum.

**(R)-tert-Butyl 3-oxo-2-phenyl-5-(phenylcarbamoyl)pyrazolidine-1-carboxylate, (R-8)**

The General Procedure described above was followed with 0.6 g (1.96 mmol) of (R)-7, 0.21 g (2 mmol, 0.29 mL) of Et\(_3\)N, 0.25 g (2 mmol, 0.25 mL) of pivaloyl chloride, 0.19 g (2 mmol, 0.19 mL) of aniline and 40 mL of THF to afford the desired N-Boc protected amide (R)-8, (0.62 g, 83% yield) as a white solid, mp 178-180 °C, \([\alpha]_D^{20} = +13.7\) (c 1, CHCl\(_3\)). \(^1\)H-\(\text{NMR}\) (CDCl\(_3\), 400 MHz): \(\delta = 1.33\) (s, 9H, C(CH\(_3\))\(_3\)), 3.20 (dd, \(J = 9.7\), 17.4 Hz, 1H, CH\(_2\)), 3.36 (dd, \(J = 1.6\), 17.4 Hz, 1H, CH\(_2\)), 5.13 (dd, \(J = 1.6\), 9.7 Hz, 1H, *CH), 7.13-7.23 (m, 2H, ArCH\(_H\)), 7.32-7.42 (m, 4H, ArCH\(_H\)), 7.51-7.57 (m, 4H, ArCH\(_H\)), 8.56 (br, 1H, NH). \(^{13}\)C-\(\text{NMR}\) (CDCl\(_3\), 100.5 MHz): \(\delta = 27.8\) (C(CH\(_3\))\(_3\)), 33.8 (CH\(_2\)), 60.0 (*CH), 85.2 (C(CH\(_3\))\(_3\)), 119.7 (2xArCH), 120.1 (2xArCH), 125.1 (ArCH), 125.7 (ArCH), 129.0 (2xArCH), 129.2 (2xArCH), 137.1 (C\(_{ipso}\)), 138.8 (C\(_{ipso}\)), 156.6 (OC=ON), 166.7 (NC=OCH\(_2\)), 168.3 (*CHC=ON). MS (IE) \(m/z\) (%): 381 (M\(^+\), 2), 281 (77), 161 (100), 119 (7), 93 (14), 57 (52). IR \(\nu_{\text{max}}\) (KBr) cm\(^{-1}\): 3446, 3231, 1733, 1697, 1677, 1516, 1316, 1158, 763. Anal. Calcd. for C\(_{21}\)H\(_{23}\)N\(_3\)O\(_4\) (381.43): C 66.13, H 6.08, N 11.02; Found: C 65.84, H 6.19, N 11.12%.

**(R)-tert-Butyl 5-(benzylcarbamoyl)-3-oxo-2-phenylpyrazolidine-1-carboxylate, (R-9)**

The General Procedure was followed with 0.6 g (1.96 mmol) of (R)-7, 0.21 g (2 mmol, 0.29 mL) of Et\(_3\)N, 0.25 g (2 mmol, 0.25 mL) of pivaloyl chloride, 0.22 g (2 mmol, 0.22 mL) of benzylamine and 40 mL of THF to obtain the N-Boc protected amide (R)-9, (0.49 g, 63% yield) as a white solid, mp 162-164 °C, \([\alpha]_D^{20} = -7.5\) (c 1, CHCl\(_3\)). \(^1\)H-\(\text{NMR}\) (CDCl\(_3\), 400 MHz): \(\delta = 1.28\) (s, 9H, C(CH\(_3\))\(_3\)), 3.15 (dd, \(J = 9.9\), 17.2 Hz, 1H, CH\(_2\)), 3.31 (dd, \(J = 1.5\), 17.2 Hz, 1H, CH\(_2\)), 4.41 (dd, \(J = 3.38\), 17.2 Hz, 1H, CH\(_2\)).
= 5.1, 14.7 Hz, 1H, CH₂Ph), 4.60 (dd, J = 6.6, 14.7 Hz, 1H, CH₂Ph), 5.05 (dd, J = 1.5, 9.6 Hz, 1H, *CH), 7.00 (br, 1H, NH), 7.13-7.24 (m, 3H, ArCH), 7.26-7.33 (m, 5H, ArCH), 7.39-7.43 (m, 2H, ArCH). ¹³C-NMR (CDCl₃, 100.5 MHz): δ = 27.7 (C(CH₃)₃), 34.0 (CH₂), 43.9 (CH₂Ph), 59.6 (*CH), 84.8 (C(CH₃)₃), 119.6 (3xArCH), 125.4 (ArCH), 127.7 (ArCH), 127.8 (ArCH), 128.7 (2xArCH), 128.8 (2xArCH), 137.4 (Cips), 138.6 (Cips), 156.5 (OC=ON), 168.4 (NC=OCH₂), 168.6 (*CH=ON). MS (IE) m/z (%): 395 (M⁺, 1), 295 (73), 189 (7), 161 (100), 105 (11), 91 (17), 57 (46), 41 (7). IR νmax (KBr) cm⁻¹: 3419, 3280, 1721, 1708, 1678, 1534, 1317, 1159, 746. Anal. Calcd. for C₂₂H₂₅N₃O₄ (395.45): C 66.82, H 6.37, N 10.63; Found: C 67.21, H 6.24, N 10.70%.

(R)- tert-Butyl 3-oxo-2-phenyl-5-[(S)-1-phenylethylcarbamoyl]pyrazolidine-1-carboxylate (R,S-10). The General Procedure was followed with 0.6 g (1.96 mmol) of (R)-7, 0.21 g (2 mmol, 0.29 mL) of Et₃N, 0.25 g (2 mmol, 0.25 mL) of pivaloyl chloride, 0.25 g (2 mmol, 0.26 mL) of (S)-α-methylbenzylamine and 40 mL of THF to obtain the N-Boc protected amide (R,S)-10 (0.63 g, 79 % yield) as a white solid, mp 172-174 °C, [α]D²⁰ = −46.2 (c 1, MeOH). ¹H-NMR (CDCl₃, 400 MHz): δ = 1.28 (s, 9H, C(CH₃)₃), 1.55 (dd, J = 7.0 Hz, 3H, *CHCH₃), 3.09 (dd, J = 9.7, 17.4 Hz, 1H, CH₂), 3.28 (dd, J = 1.8, 17.4 Hz, 1H, CH₂), 5.01 (dd, 1H, J = 1.7, 9.7 Hz), 5.13 (dq, J = 7.2, 7.9 Hz, 1H, NH*CHCH₃), 6.96 (d, J = 8.1 Hz, 1H, NH), 7.10-7.15 (m, 1H, ArCH), 7.17-7.30 (m, 9H, ArCH). ¹³C-NMR (CDCl₃, 100.5 MHz): δ = 21.7 (*CHCH₃), 27.8 (C(CH₃)₃), 33.8 (CH₂), 49.4 (*CHCH₃), 59.5 (*CH), 84.8 (C(CH₃)₃), 119.7 (2xArCH), 125.5 (ArCH), 126.1 (2xArCH), 127.7 (ArCH), 128.8 (2xArCH), 138.6 (Cips), 142.5 (Cips), 156.4 (OC=ON), 167.7 (NC=OCH₂), 168.6 (*CH=ON). MS (IE) m/z (%): 409 (M⁺, 2), 309 (53), 205 (42), 161 (100), 120 (5), 105 (85), 77 (7), 57 (58). IR νmax (KBr) cm⁻¹: 3419, 3318, 1723, 1703, 1677, 1522, 1314, 1158, 755. Anal. Calcd. for C₂₃H₂₅N₃O₄ (409.48): C 67.46, H 6.65, N 10.26; Found: C 67.13, H 6.87, N 10.35%.

(R)- tert-Butyl 5-[(S)-1-hydroxybutan-2-ylcarbamoyl]-3-oxo-2-phenylpyrazolidine-1-carboxylate, (R,S-11). The General Procedure was followed with 0.6 g (1.96 mmol) of (R)-7, 0.21 g (2 mmol, 0.29 mL) of Et₃N, 0.25 g (2 mmol, 0.25 mL) of pivaloyl chloride, 0.18 g (2 mmol, 0.2 mL) of (S)-2-amino-1-butanol and 40 mL of THF to obtain the N-Boc protected amide (R,S)-11 (0.58 g, 79 % yield) as a white solid, mp 180-182 °C, [α]D²⁰ = +6.6 (c 1, MeOH). ¹H-NMR (CDCl₃ + DMSO-d₆ 5:1 v/v, 300 MHz): δ = 0.83 (t, J = 7.5 Hz, 3H, CH₂CH₃), 1.21 (s, 9H, C(CH₃)₃), 1.39-1.62 (m, 2H, CH₂CH₃), 2.87 (d, J = 17.1 Hz, 1H, CH₂), 3.12 (dd, J = 9.6, 17.1 Hz, 1H, CH₂), 3.43 (dd, J = 4.3, 10.9 Hz, 1H, *CHCH₂OH), 4.49 (dd, 4.3, 10.9 Hz, 1H, *CHCH₂OH), 3.65-3.79 (m, 1H, *CHCH₂OH), 4.97 (d, J = 9.0 Hz, 1H, *CH), 7.03-7.10 (m, 1H, ArCH), 7.23-7.29 (m, 2H, ArCH), 7.39 (d, J = 8.4 Hz, NH), 7.45-7.48 (m, 2H, ArCH). ¹³C-NMR (CDCl₃ + DMSO-d₆ 5:1 v/v, 75.5 MHz): δ = 10.6 (CH₂CH₃), 24.1 (CH₂CH₃), 27.8 (C(CH₃)₃), 34.8 (CH₂), 52.9 (*CHCH₂OH), 59.0 (*CH), 63.0 (*CHCH₂OH), 83.7 (C(CH₃)₃), 120.5 (2xArCH), 125.3 (ArCH), 128.5 (2xArCH), 138.8 (Cips), 155.8 (OC=ON), 168.5 (NC=OCH₂), 168.8 (*CH=ON). MS (IE) m/z (%): 377 (M⁺, 2), 277 (46), 171 (26), 161 (100), 108 (14), 57 (56), 41 (8). IR νmax (KBr) cm⁻¹: 3496, 3320, 2935, 1736, 1709, 1684, 1547, 1307,
(S)-tert-Butyl 3-oxo-2-phenyl-5-(phenylcarbamoyl)pyrazolidine-1-carboxylate, (S)-8. The General Procedure was followed with 0.55 g (1.79 mmol) of (S)-7, 0.19 g (1.88 mmol, 0.27 mL) of Et3N, 0.23 g (1.88 mmol, 0.23 mL) of pivaloyl chloride, 0.17 g (1.88 mmol, 0.17 mL) of aniline and 35 mL of THF to obtain the N-Boc protected amide (S)-8 (0.6 g, 88% yield) as a white solid, mp 176-178 °C, [α]D20 = −14.2 (c 1, CHCl3). 1H- NMR (CDCl3, 400 MHz): δ = 1.32 (s, 9H, C(CH3)3), 3.19 (dd, J = 9.7, 17.4 Hz, 1H, CH2), 3.36 (dd, J = 1.8, 17.6 Hz, 1H, CH2), 5.13 (dd, J = 1.7, 9.7 Hz, 1H, *CH), 7.12-7.22 (m, 2H, ArCH), 7.31-7.42 (m, 4H, ArCH), 7.49-7.52 (m, 2H, ArCH), 8.55 (br, 1H, NH). 13C- NMR (CDCl3, 100.5 MHz): δ = 27.8 (C(CH3)3), 33.7 (CH2), 59.9 (*CH), 85.1 (C(CH3)3), 119.6 (2xArCH), 120.0 (2xArCH), 125.0 (ArCH), 125.6 (ArCH), 128.9 (2xArCH), 129.2 (2xArCH), 137.1 (Cipso), 138.8 (Cipso), 156.5 (OC=ON), 166.7 (NC=OCH2), 168.2 (C=ONPh). MS (IE) m/z (%): 381 (M+, 1), 281 (75), 175 (6), 161 (100), 119 (5), 93 (11), 77 (5), 57 (62). IR νmax (KBr) cm⁻1: 3446, 3231, 1733, 1697, 1678, 1516, 1316, 1158, 763.

(S)-tert-Butyl 5-(benzylcarbamoyl)-3-oxo-2-phenylpyrazolidine-1-carboxylate, (S)-9. The General Procedure was followed with 0.55 g (1.79 mmol) of (S)-7, 0.19 g (1.88 mmol, 0.27 mL) of Et3N, 0.23 g (1.88 mmol, 0.23 mL) of pivaloyl chloride, 0.20 g (1.88 mmol, 0.20 mL) of benzylamine and 35 mL of THF to obtain the N-Boc protected amide (S)-9 (0.57 g, 81% yield) as a white solid, mp 158-160 °C, [α]D20 = +8.0 (c 1, CHCl3). 1H- NMR (CDCl3, 400 MHz): δ = 1.28 (s, 9H, C(CH3)3), 3.15 (dd, J = 9.9, 17.2 Hz, 1H, CH2), 3.32 (dd, J = 1.5, 17.2 Hz, 1H, CH2), 4.41 (dd, J = 5.1, 14.6 Hz, 1H, CH2Ph), 4.61 (dd, J = 6.6, 14.6 Hz, 1H, CH2Ph), 5.05 (dd, J = 1.6, 9.7 Hz, 1H, *CH), 7.00 (br, 1H, NH), 7.13-7.34 (m, 8H, ArCH), 7.38-7.43 (m, 2H, ArCH). 13C- NMR (CDCl3, 100.5 MHz): δ = 27.8 (C(CH3)3), 34.1 (CH2), 44.0 (CH2Ph), 59.7 (*CH), 85.0 (C(CH3)3), 119.6 (2xArCH), 125.5 (ArCH), 127.7 (2xArCH), 127.8 (ArCH), 128.8 (2xArCH), 128.9 (2xArCH), 137.4 (Cipso), 138.7 (Cipso), 156.5 (OC=ON), 168.4 (NC=OCH2), 168.7 (C=ONPh). MS (IE) m/z (%): 395 (M+, 1), 295 (57), 189 (6), 161 (100), 105 (10), 91 (13), 57 (58), 41 (6). IR νmax (KBr) cm⁻1: 3419, 3280, 1721, 1708, 1678, 1534, 1317, 1159, 746.

(S)-tert-Butyl 3-oxo-2-phenyl-5-[(S)-1-phenylethylcarbamoyl]pyrazolidine-1-carboxylate, (S,S)-10. The General Procedure was followed with 0.55 g (1.79 mmol) of (S)-7, 0.19 g (1.88 mmol, 0.27 mL) of Et3N, 0.23 g (1.88 mmol, 0.23 mL) of pivaloyl chloride, 0.23 g (1.88 mmol, 0.24 mL) of (S)-α-methylbenzylamine (S)-5 and 35 mL of THF to obtain the N-Boc protected amide (S,S)-10 (0.51 g, 69% yield) as a white solid, mp 164-166 °C, [α]D20 = −93.1 (c 1, MeOH). 1H- NMR (CDCl3, 400 MHz): δ = 1.31 (s, 9H, C(CH3)3), 1.44 (d, J = 6.8 Hz, 3H, *CHCH3), 3.13 (dd, J = 9.6, 17.3 Hz, 1H, CH2), 3.25 (dd, J = 1.8, 17.4 Hz, 1H, CH2), 4.98 (dd, J = 1.8, 9.5 Hz, 1H, *CH), 5.09 (dq, J = 7.0, 7.3 Hz, 1H, NH*CHCH3), 6.96 (d, J = 7.7 Hz, 1H, NH), 7.17-7.43 (m, 8H, ArCH), 7.50-7.56 (m, 2H, ArCH). 13C- NMR (CDCl3, 100.5 MHz): δ = 22.0 (*CHCH3), 27.8 (C(CH3)3), 34.4 (CH2), 49.5 (*CHCH3), 59.8 (*CH), 84.9 (C(CH3)3), 119.3 (2xArCH), 125.6 (ArCH), 126.2 (2xArCH), 127.8 (ArCH), 128.9 (2xArCH), 129.0 (2xArCH), 138.8 (Cipso), 142.6 (Cipso), 156.5 (OC=ON), 167.9 (NC=OCH2), 168.6 (*CH=ON). MS (IE)
$m/z$ (%): 409 (M$^+$, 1), 309 (52), 205 (35), 161 (100), 119 (4), 105 (88), 77 (6), 57 (70), 41 (6). IR $v_{\text{max}}$ (KBr) cm$^{-1}$: 3339, 2919, 1739, 1720, 1675, 1532, 1306, 1153, 756. HRMS (ESI-TOF) calculated for C$_{23}$H$_{27}$N$_2$O$_4$ + H$^+$: 410.2074; Found: 410.2074.

(S)-tert-Butyl 5-[(S)-1-hydroxybutan-2-ylcarbamoyl]-3-oxo-2-phenylpyrazolidine-1-carboxylate, (S,S-11). The General Procedure was followed with 0.55 g (1.79 mmol) of (S)-7, 0.19 g (1.88 mmol, 0.27 mL) of Et$_3$N, 0.23 g (1.88 mmol, 0.23 mL) of pivaloyl chloride, 0.17 g (1.88 mmol, 0.18 mL) of (S)-2-aminobutanol-1-ol and 35 mL of THF to obtain the N-Boc protected amide (S,S)-11 (0.52 g, 77 % yield) as a white solid, mp 174-176 °C, [$\alpha$]$_D^{20}$ = – 31.0 (c 1, MeOH). $^1$H- NMR (CDCl$_3$, 400 MHz): $\delta$ = 0.79 (t, $J$ = 7.5 Hz, 3H, CH$_2$CH$_3$), 1.30 (s, 9H, C(CH$_3$)$_3$), 1.34-1.37 (m, 1H, CH$_2$CH$_3$), 1.51-1.63 (m, 1H, CH$_2$CH$_3$), 2.48 (br, 1H, OH), 3.15 (dd, $J$ = 9.2, 17.2 Hz, 1H, CH$_2$), 3.24 (dd, $J$ = 2.0, 17.4 Hz, 1H, CH$_2$), 3.61-3.69 (m, 1H, *CHCH$_2$OH), 3.69-3.77 (m, 1H, *CHCH$_2$OH), 3.82-3.92 (m, 1H, *CHCH$_2$OH), 5.03 (dd, $J$ = 2.0, 9.3 Hz, 1H, *CH), 6.86 (d, $J$ = 8.0 Hz, 1H, NH), 7.14-7.20 (m, 1H, ArCH), 7.33-7.40 (m, 2H, ArCH), 7.49-7.56 (m, 2H, ArCH). $^{13}$C- NMR (CDCl$_3$, 100.5 MHz): $\delta$ = 10.4 (CH$_2$CH$_3$), 24.2 (CH$_2$CH$_3$), 27.8 (C(CH$_3$)$_3$), 34.5 (CH$_3$), 53.5 (*CHCH$_2$OH), 59.7 (*CH), 64.6 (*CHCH$_2$OH), 85.0 (C(CH$_3$)$_3$), 119.1 (2xArCH), 125.4 (ArCH), 128.9 (2xArCH), 138.7 (C$_{ipso}$), 156.5 (OC=ON), 168.4 (NC=OCH$_2$), 169.3 (*CHC=ON). MS (IE) $m/z$ (%): 377 (M$^+$, 1), 277 (41), 218 (3), 171 (17), 161 (100), 108 (8), 77 (3), 57 (68), 41 (5). IR $v_{\text{max}}$ (KBr) cm$^{-1}$: 3442, 3298, 2980, 1720, 1698, 1655, 1543, 1314, 1160, 769.

**General procedure for the N-tert-butoxycarbonyl group removal**

The required N-Boc-amide was dissolved in CH$_2$Cl$_2$ and 18 equiv. of trifluoroacetic acid was added. The resulting reaction mixture was stirred during 2 h at room temperature and then the mixture was extracted five times with a saturated solution of NaHCO$_3$. The aqueous phase was extracted twice with CH$_2$Cl$_2$ and the organic phase was washed with brine, dried with anhyd. Na$_2$SO$_4$ and concentrated in the rotary evaporator. The corresponding product was recrystallised from a mixture of hexane-EtOAc (95:5 v/v) or purified by column chromatography. The products were dried at 40 °C under vacuum.

(R)-5-Oxo-N, 1-diphenylpyrazolidine-3-carboxamide, (R-12). The General Procedure was followed with 0.54 g (1.41 mmol) of (R)-8 to obtain amide (R)-12. This product was recrystallised from hexane-EtOAc (95:5 v/v) to give 0.38 g (96% yield) of (R)-12 as a white solid, mp 190-192 °C, [$\alpha$]$_D^{20}$ = + 136.5 (c 1, CHCl$_3$). $^1$H- NMR (CDCl$_3$, 400 MHz): $\delta$ = 3.10 (dd, $J$ = 9.0, 17.0 Hz, 1H, CH$_2$), 3.18 (dd, $J$ = 4.2, 17.0 Hz, 1H, CH$_2$), 4.23 (ddd, $J$ = 4.4, 6.4, 8.8 Hz, 1H, *CH), 6.00 (d, $J$ = 5.8 Hz, 1H, PhNNH), 7.04-7.15 (m, 2H, ArCH), 7.23-7.37 (m, 4H, ArCH), 7.44-7.48 (m, 2H, ArCH), 7.82-7.87 (m, 2H, ArCH), 9.32 (br, 1H, NH). $^{13}$C- NMR (CDCl$_3$, 100.5 MHz): $\delta$ = 37.5 (CH$_2$), 56.0 (*CH), 117.9 (2xArCH), 119.8 (2xArCH), 124.60 (ArCH), 124.63 (ArCH), 128.9 (2xArCH), 129.0 (2xArCH), 137.3 (C$_{ipso}$), 138.6 (C$_{ipso}$), 168.7 (NC=OCH$_2$), 169.6 (C=ONPh). MS (IE) $m/z$ (%): 282 (M$^+$+1, 9), 281 (M$^+$, 100), 280 (M$^+$–1, 24), 206 (8), 161 (93), 93 (52), 66 (3). IR $v_{\text{max}}$ (KBr) cm$^{-1}$: 3446, 3313, 2421, 1708, 1687, 1531,
(R)-N-Benzyl-5-oxo-1-phenylpyrazolidine-3-carboxamide, (R-13). The General Procedure was followed with 0.43 g (1.09 mmol) of (R)-9 to obtain crude amide (R)-13, which was recrystallised from hexane-EtOAc (95:5 v/v) to afford 0.27 g (85 % yield) of (R)-13 as a white solid, mp 158-160 °C, [α]D²⁰ = + 86.1 (c 1, CHCl₃). ¹H- NMR (CDCl₃, 400 MHz): δ = 3.14 (dd, J = 9.2, 17.2 Hz, 1H, CH₂), 3.26 (dd, J = 2.9, 17.2 Hz, 1H, CH₂), 4.20 (dd, J = 2.9, 6.2, 9.5 Hz, 1H, *CH), 4.41 (dd, J = 5.7, 14.8 Hz, 1H, CH₂Ph), 4.50 (dd, 1H, J = 5.8, 15.0 Hz), 5.33 (d, J = 6.6 Hz, 1H, PhNNH), 7.13-7.19 (m, 3H, ArCH), 7.25-7.29 (m, 3H, ArCH), 7.33-7.39 (m, 2H, ArCH), 7.48 (br, 1H, NHCH₂Ph), 7.76-7.80 (m, 2H, ArH). ¹³C- NMR (CDCl₃, 100.5 MHz): δ = 37.6 (CH₃), 43.4 (CH₂Ph), 55.7 (*CH), 118.1 (2xArCH), 124.6 (ArCH), 127.4 (2xArCH), 127.5 (ArCH), 128.7 (2xArCH), 128.9 (2xArCH), 137.8 (C_{ipso}), 138.6 (C_{ipso}), 169.8 (NC=OCH₂), 170.3 (C=ONCH₂Ph). MS (IE) m/z (%): 296 (M⁺+1, 9), 295 (M⁺, 49), 189 (7), 161 (100), 108 (6), 91 (6). IR νmax (KBr) cm⁻¹: 3448, 3390, 3210, 2171, 1684, 1594, 1361, 1007, 762.

(R)-5-Oxo-1-phenyl-N-[(S)-1-phenylethyl]pyrazolidine-3-carboxamide, (R,S-14). The General Procedure was followed with 0.55 g (1.34 mmol) of (R,S)-10 to obtain crude amide (R,S)-14, which was recrystallised from hexane-EtOAc (95:5 v/v) to give 0.41 g (99 % yield) of (R,S)-14 as a white solid, mp 118-120 °C, [α]D²⁰ = + 73.1 (c 1, CHCl₃). ¹H- NMR (CDCl₃, 400 MHz): δ = 1.45 (d, J = 6.6 Hz, 3H, *CH₂), 2.99 (dd, J = 8.6, 17.4 Hz, 1H, CH₂), 3.10 (dd, J = 3.1, 17.0 Hz, 1H, CH₂), 4.04-4.14 (m, 1H, *CH), 5.04 (dq, 1H, J = 7.3, 7.3 Hz, *CH₂CH₃), 5.54 (br, 1H, PhNNH), 7.02-7.07 (m, 2H, ArCH), 7.11-7.19 (m, 4H, ArCH), 7.30-7.37 (m, 2H, ArCH), 7.58 (br, 1H, NH*CHCH₃), 7.69-7.75 (m, 2H, ArCH). ¹³C- NMR (CDCl₃, 100.5 MHz): δ = 22.2 (*CH₂CH₃), 37.4 (CH₃), 48.9 (*CH₂CH₃), 56.0 (*CH), 118.1 (2xArCH), 124.9 (ArCH), 125.6 (2xArCH), 127.4 (ArCH), 128.7 (2xArCH), 129.0 (2xArCH), 138.5 (C_{ipso}), 142.6 (C_{ipso}), 169.1 (NC=OCH₂), 169.8 (*CH=ON). MS (IE) m/z (%): 310 (M⁺+1, 18), 309 (M⁺, 83), 205 (100), 161 (98), 105 (81) 77 (7). IR νmax (KBr) cm⁻¹: 3313, 3238, 3195, 1687, 1657, 1528, 1360, 755, 699. HRMS (ESI-TOF) calculated for C₁₅H₁₉N₂O₂ + H⁺: 310.1550; Found: 310.1553.

(R)-N-[((S)-1-Hydroxybutan-2-yl]-5-oxo-1-phenylpyrazolidine-3-carboxamide, (R,S-15). The General Procedure was followed with 0.49 g (1.3 mmol) of (R,S)-11 to obtain crude amide (R,S)-15, which was purified by column chromatography using a mixture of EtOAc-hexane (8:2 v/v) as eluent to give 0.26 g (72 % yield) of (R,S)-15 as a white solid, mp 106-108 °C, [α]D²⁰ = + 53.0 (c 1, MeOH). ¹H- NMR (CDCl₃, 300 MHz): δ = 0.91 (t, J = 7.4 Hz, 3H, CH₂CH₃), 1.43-1.67 (m, 2H, CH₂CH₃), 2.50 (br, 1H, OH), 3.04 (dd, J = 9.0, 17.3 Hz, 1H, CH₂), 3.15 (dd, J = 4.7, 17.2 Hz, 1H, CH₂), 3.47-3.57 (m, 2H, CH₂OH), 3.73-3.84 (m, 1H, *CH₂CHOH), 4.06-4.16 (m, 1H, *CH), 5.50 (d, J = 6.9 Hz, 1H, PhNNH), 7.12-7.17 (m, 1H, ArCH), 7.33-7.39 (m, 3H, C=ONH, ArCH), 7.77-7.84 (m, 2H, ArCH). ¹³C- NMR (CDCl₃, 75.5 MHz): δ = 10.6 (CH₂CH₃), 24.2 (CH₂CH₃), 37.6 (CH₃), 53.3 (*CH₂CHOH), 55.8 (*CH), 64.4 (*CH₂CHOH), 118.4 (2xArCH), 125.1 (ArCH), 129.2 (2xArCH), 138.3 (C_{ipso}), 169.8 (NC=OCH₂), 170.6 (*CH=ON). MS (IE) m/z (%): 278 (M⁺+1, 3), 277 (M⁺, 15), 171 (23), 161 (100), 153 (11), 108 (14), 58 (14), 43 (5).
IR νmax (KBr) cm⁻¹: 3328, 3244, 2876, 1693, 1646, 1548, 1497, 1362, 1220, 756. HRMS (ESI-TOF) calculated for C₁₄H₁₀N₃O₃ + H⁺: 278.1499; Found: 278.1498.

**[(S)-5-Oxo-N-1-diphenylpyrazolidine-3-carboxamide, (S-12)]**: The General Procedure was followed with 0.56 g (1.46 mmol) of [(S)-8] to obtain crude amide (S-12), which was recrystallised from hexane-EtOAc (95:5 v/v) to afford 0.38 g (92% yield) of (S-12) as a white solid, mp 188-190 °C, [α]D²⁰ = −132.7 (c 1, CHCl₃). ¹H-NMR (CDCl₃, 400 MHz): δ = 3.21 (dd, J = 9.7, 17.6 Hz, 1H, CH₂), 3.29 (dd, J = 2.9, 17.6 Hz, 1H, CH₂), 4.28 (d, J = 8.8 Hz, 1H, *CH), 5.48 (br, 1H, PhNNH), 7.10-7.22 (m, 2H, ArCH), 7.29-7.35 (m, 2H, ArCH), 7.39-7.53 (m, 4H, ArCH), 7.86-7.91 (m, 2H, ArCH), 9.11 (br, 1H, NHPh). ¹³C-NMR (CDCl₃, 100.5 MHz): δ = 37.4 (CH₂), 55.9 (*CH), 117.9 (2xArCH), 119.8 (2xArCH), 124.5 (ArCH), 124.6 (ArCH), 128.9 (2xArCH), 129.0 (2xArCH), 137.3 (Cipso), 138.6 (Cipso), 168.7 (NC=OCH₂), 169.6 (C=ONPh). MS (EI) m/z (%): 282 (M⁺ + 1, 19), 281 (M⁺, 83), 175 (16), 161 (100), 134 (11), 93 (19), 77 (6), 65 (3). IR νmax (KBr) cm⁻¹: 3446, 3313, 2345, 1708, 1687, 1531, 1360, 1065, 756.

**[(S)-N-Benzyl-5-oxo-1-phenylpyrazolidine-3-carboxamide, (S-13)]**: The General Procedure was followed with 0.53 g (1.34 mmol) of (S)-9 to obtain crude amide (S-13), which was recrystallised from hexane-EtOAc (95:5 v/v) to give 0.37 g (94% yield) of (S-13) as a white solid, mp 156-158 °C, [α]D²⁰ = −85.6 (c 1, CHCl₃). ¹H-NMR (CDCl₃, 400 MHz): δ = 3.11 (dd, J = 9.5, 17.2 Hz, 1H, CH₂), 3.23 (dd, J = 3.3, 17.2 Hz, 1H, CH₂), 4.17 (ddd, J = 3.1, 6.4, 9.5 Hz, 1H, *CH), 4.40 (dd, J = 5.9, 15.0 Hz, 1H, CH₂Ph), 4.49 (dd, J = 5.9, 15.0 Hz, 1H, CH₂Ph), 5.36 (d, J = 6.6 Hz, 1H, PhNNH), 7.12-7.18 (m, 3H, ArCH), 7.24-7.28 (m, 3H, ArCH), 7.32-7.38 (m, 2H, ArCH), 7.48 (br, 1H, NHCH₂Ph), 7.75-7.80 (m, 2H, ArCH). ¹³C-NMR (CDCl₃, 100.5 MHz): δ = 37.5 (CH₂), 43.4 (CH₂Ph), 55.7 (*CH), 118.1 (2xArCH), 124.6 (ArCH), 127.4 (2xArCH), 127.5 (ArCH), 128.7 (2xArCH), 128.9 (2xArCH), 137.3 (Cipso), 138.5 (Cipso), 169.7 (NC=OCH₂), 170.2 (C=ONCH₂Ph). MS (EI) m/z (%): 296 (M⁺ + 1, 20), 295 (M⁺, 100), 253 (4), 189 (5), 161 (93), 91 (10), 77 (6). IR νmax (KBr) cm⁻¹: 3446, 3398, 3210, 2331, 1684, 1594, 1361, 1007, 762. Anal. Calcd. for C₁₇H₁₇N₃O₂ (295.34): C 69.14, H 5.80, N 14.23; Found: C 69.46, H 6.00, N 14.44%.

**[(S)-5-Oxo-1-phenyl-N-[(S)-1-phenylethyl]pyrazolidine-3-carboxamide, (S,S-14)]**: The General Procedure was followed with 0.475 g (1.16 mmol) of (S,S)-10 to obtain crude amide (S,S)-14, which was recrystallised from hexane-EtOAc (95:5 v/v) to give 0.36 g (99% yield) of (S,S)-14 as a white solid, mp 152-154 °C, [α]D²⁰ = −83.6 (c 1, CHCl₃). ¹H-NMR (CDCl₃, 400 MHz): δ = 1.36 (d, J = 7.0 Hz, 3H, *CHCH₃), 3.00 (dd, J = 9.5, 17.2 Hz, 1H, CH₂), 3.13 (ddd, J = 2.9, 17.2 Hz, 1H, CH₂), 4.04 (ddd, J = 3.1, 6.0, 9.3 Hz, 1H, *CH), 5.02 (dq, J = 7.0, 7.2 Hz, 1H, *CHCH₃), 5.40 (d, J = 6.2 Hz, 1H, PhNNH), 7.14-7.20 (m, 1H, ArCH), 7.24-7.42 (m, 7H, ArCH), 7.46 (br, 1H, NH*CHCH₃), 7.78-7.85 (m, 1H, ArCH). ¹³C-NMR (CDCl₃, 100.5 MHz): δ = 22.0 (*CHCH₃), 37.4 (CH₂), 49.2 (*CHCH₃), 55.8 (*CH), 118.0 (2xArCH), 124.9 (ArCH), 126.1 (2xArCH), 127.7 (ArCH), 128.9 (2xArCH), 129.1 (2xArCH), 138.6 (Cipso), 142.9 (Cipso), 169.1 (NC=OCH₂), 169.7 (*CHC=ON). MS (EI) m/z (%): 309 (M⁺, 43), 282 (5), 205 (73), 161 (100), 105 (95), 77 (7). IR νmax (KBr) cm⁻¹: 3446, 3314, 3235, 2358, 1963, 1691, 1652, 1550.
(S)-N′-[S)-(1-Hydroxybutan-2-yl]-5-oxo-1-phenylpyrazolidine-3-carboxamide, (S,S-15). The General Procedure was followed with 0.46 g (1.22 mmol) of (S,S)-11 to obtain crude amide (S,S)-15, which was purified by gradient column chromatography [EtOAc → EtOAc-MeOH (8:2 v/v)] to give 0.38 g (81 % yield) of (S,S)-15 as a white solid, mp 184-186 °C, [α]D20 = –100.0 (c 1, MeOH).

1H- NMR (CDCl3 + DMSO-d6 5:1 v/v, 400 MHz) δ: 0.63 (t, J = 7.5 Hz, 3H, CH2C3H3), 1.18-1.27 (m, 1H, CH2CH3), 1.39-1.50 (m, 1H, CH2CH3), 2.93 (dd, J = 4.2, 16.7 Hz, 1H, CH2), 2.98 (dd, J = 8.8, 16.5 Hz, 1H, CH2), 3.42-3.46 (m, 2H, CH2OH), 3.64-3.72 (m, 1H, *CHCH2OH), 4.05 (dd, J = 4.2, 8.6 Hz, 1H, *CH), 7.01-7.06 (m, 1H, ArCH), 7.24-7.29 (m, 2H, ArCH), 7.60 (d, J = 8.4 Hz, 1H, =ONH), 7.75-7.80 (m, 2H, ArCH). 13C- NMR (CDCl3 + DMSO-d6 5:1 v/v, 100.5 MHz): δ = 10.3 (CH2C3H3), 24.2 (CH2CH3), 37.7 (CH2), 52.7 (*CHCH2OH), 55.7 (*CH), 63.4 (*CHCH2OH), 118.2 (2xArCH), 124.3 (ArCH), 128.8 (2xArCH), 139.0 (Cipso), 170.2 (NC=OCH3), 170.5 (*CHC=ON). MS (IE) m/z (%): 277 (M+, 22), 218 (2), 171 (23), 161 (100), 119 (14), 108 (16), 58 (17), 43 (5). IR νmax (KBr) cm⁻1: 3426, 3275, 3213, 2961, 2170, 1688, 1630, 1361, 1072, 756.

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References and Notes

10. For a recent example, see: Ávila-Ortiz, C. G.; Reyes-Rangel, G.; Juaristi, E. *Tetrahedron* 2005, 61, 8372.
12. Dimethyl fumarate was obtained as a white solid, mp 105-106 °C in agreement with literature data (mp 102-106 °C, see: *Aldrich Catalog of Fine Chemicals*, Sigma-Aldrich Chemical Company, Milwaukee, 2009-2010; p 1131).
14. Crystal data for 4: C_{18}H_{31}N_{3}O_{3}, monoclinic, space group P 2(1), a = 11.9112(3) Å, b = 6.4941(2) Å, c = 12.0419(4) Å, α = γ = 90°, β = 117.880(2) °, V = 823.35(4) Å³, crystal size: 0.4x0.1x0.075 mm³, R1 = 0.0424 (wR2 = 0.1028). Crystal data for 5: C_{11}H_{12}N_{2}O_{3}, monoclinic, space group P 2(1)/c, a = 9.1982(2) Å, b = 7.2755(2) Å, c = 16.6637(4) Å, α = γ = 90°, β = 100.9830(10) °, V = 1094.73(5) Å³, crystal size: 0.6x0.27x0.12 mm³, R1 = 0.0404 (wR2 = 0.0943). Crystal data for 11: C_{19}H_{27}N_{2}O_{5}, orthorhombic, space group P 2(1)2(1)2(1), a = 6.1885(1) Å, b = 17.8721(5) Å, c = 17.8860(4) Å, α = β = γ = 90°, V = 1978.218(77) Å³, crystal size: 0.35x0.17x0.12 mm³, R1 = 0.0740 (wR2 = 0.1516). Crystal data for 12: C_{16}H_{15}N_{3}O_{2}, monoclinic, space group P 2(1), a = 8.7768(3) Å, b = 6.1093(12) Å, c = 13.596(3) Å, α = γ = 90°, β = 101.76(3)°, V = 713.7(2) Å³, crystal size: 0.5x0.25x0.25 mm³, R1 = 0.0412 (wR2 = 0.1042). Crystal data for 15: C_{14}H_{19}N_{3}O_{3}, orthorhombic, space group P 2(1)2(1)2(1), a = 6.4721(2) Å, b = 10.9192(3) Å, c = 20.4803(6) Å, α = β = γ = 90°, V = 1447.35(7) Å³, crystal size: 0.27x0.1x0.1 mm³, R1 = 0.0471 (wR2 = 0.0972). CCDC 758525 (for 4), CCDC 758526 (for 5), CCDC 758527 (for 11), CCDC 758528 (for 12) and CCDC 758529 (for 15) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.