Optical Resolution of 5-Oxo-1-phenyl-pyrazolidine-3-carboxylic Acid as a New Organocatalyst for Organic Reactions

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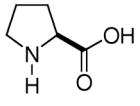
Optical resolution of racemic 5-oxo-1-phenyl-pyrazolidine-3-carboxylic acid **2** with L-amino acid methyl ester via the diastereomers formation was investigated. Treatment of racemic 5-oxo-1-phenyl-pyrazolidine-3-carboxylic acid **2** with L-valine methyl ester gave diastereomers with a total yield of 86%. The diastereomeric dipeptides can be easily separated by flash column chromatography. Acidic cleavage of the derived diastereomers gave both the optically pure (+)-(*R*)- and (-)-(*S*)-5-oxo-1-phenyl-pyrazolidine-3-carboxylic acid ((+)-(*R*)-**2** and (-)-(*S*)-**2**) with a total yield of 94% and 95%, respectively.

Keywords: Optical resolution; Organocatalyst; 5-Oxo-1-phenyl-pyrazolidine-3-carboxylic acid; L-Amino acid.

INTRODUCTION

The rapid development of metal free small molecules for various stereoselective catalysis requires an increasing demand of novel structural organocatalysts.[1] The catalytical enantioselective transformations for the preparation of useful intermediates with structural diversity is an ongoing endeavor in organic synthesis. Recently, asymmetric synthesis by using optically pure organocatalysts has attracted much attention for the construction of various C-C bonds, such as aldol,[2] Mannich,[3] Michael addition,[4] Diels-Alder Reactions,[5] etc. Small organic molecules such as L-proline **1** and its derivatives have emerged as a viable strategy for stereochemical reactions since 2000.[6] Many reaction types have been studied and high to excellent stereoselectivities were achieved. The mechanistic explanation was proposed that involves the stabilization of a transition state conformation with hydrogen bonding.[7] Optical resolution of racemic materials is a conventional approach to prepare enantiomeric pure chiral compounds.[8] In this communication, we describe an efficient optical resolution of racemic 5-oxo-1-phenyl-pyrazolidine-3-carboxylic acid **2** with L-amino acid methyl ester to provide diastereomers with high overall material yield. The diastereomeric compounds were then separated by flash column chromatography and further hydrolysis to give both enantiomers with high optical purity as measured by optical rotation.



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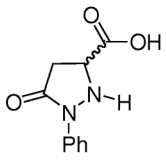


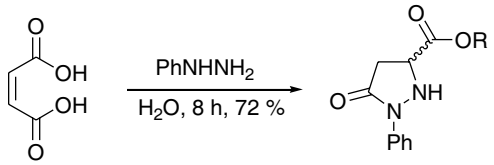
2

(+)-(*R*)-**2** : α-COOH
(-)-(*S*)-**2** : β-COOH

RESULTS AND DISCUSSION

The starting racemic 5-oxo-1-phenyl-pyrazolidine-3-carboxylic acid **2** can be easily prepared by the reported procedure.[9] Treatment of maleic acid with phenylhydrazine under refluxing conditions in H_2O for 8 h provided the desired product with 72% yield (Scheme I). The chemical structure of **2** was determined by ^{1}H-, ^{13}C-NMR and HRMS analyses and further confirmed by single crystal X-ray analysis of its methyl ester derivative **3** (conc. H_2SO_4, MeOH, reflux 3 h, 65% yield).

Scheme I



2 : R = H
3 : R = Me

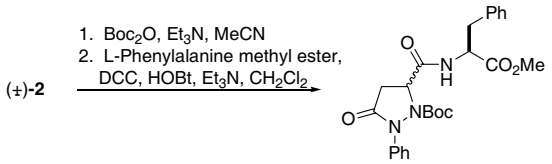
An efficient resolution of diastereomeric mixtures has been documented on the difference in solubility of the

pair salts.[10] Initially, we studied the possibility to co-crystallize one of the diastereomeric salts of 5-oxo-1-phenyl-pyrazolidine-3-carboxylic acid **2** using different resolving agents (e.g. (*R,R*)- and (*S,S*)-1,2-diamino-cyclohexane, and Quinine). Many attempts that failed led us to seek the covalent bond formation of diastereomers and subsequent separation. We first screened various L-amino acid methyl esters for the reason that the dipeptide–like compounds can serve as useful organocatalysts when the methyl ester functional group was hydrolyzed to the corresponding carboxylic acid.[11] Toward this end, racemic 5-oxo-1-phenyl-pyrazolidine-3-carboxylic acid **2** was treated with di-*tert*-butyl dicarbonate as its *N*-Boc protected compound. Amide bond formation of the Boc-protected **2** was then treated with various L-amino acid methyl esters in the presence of coupling reagents (*N*,*N*-dicyclohexylcarbodiimide (DCC), 3-ethyl-1-(3-dimethyl-amino-propyl)-carbodiimide·HCl (EDC) and 1-hydroxybenzotriazole (HOBt)) under the standard conditions. The use of L-phenylalanine methyl ester afforded the desired diastereomeric pair of products with moderate yield (49%) when DCC (1.1 equiv) and HOBt (1.1 equiv) were used (entry 1). We then fine-tuned the reaction conditions by varying the amount of the coupling reagents and studying the temperature effect of the amide bond formation. A comparable result was obtained when an excess of DCC (4.0 equiv) was used while the material yield decreased in the absence of HOBt (entries 2 and 3). On the other hand, suitable amounts of DCC (1.2 equiv) and HOBt (0.2 equiv) used at ambient temperature afforded the desired product with a total yield of 65% (entry 4). A slight improvement in chemical yield was observed when the reaction was carried out at 0 °C (entry 5). Finally, an excellent yield was obtained when racemic compound **2** was treated with EDC (1.2 equiv) and HOBt (0.2 equiv) at 0 °C (entry 6). The reaction can be scaled up for gram quantities (30 g) to give the desired product in 79% total yield.

The proximity in polarity of the corresponding diastereomers [(R_f = 0.21 and 0.17 (hexanes/EtOAc = 3/1), respectively] cause the separation (flash column chromatography) to be a challenging task. In addition, many attempts to crystallize both or either of the diastereomers for absolute stereochemistry determination failed.

We then turned our attention to the synthesis of other pairs of diastereomers by using other L-amino acid methyl esters under the optimum reaction conditions with the hope of crystallization of any diastereomer for stereochemistry

Table 1. Optical resolution of racemic 5-oxo-1-phenyl-pyrazolidine-3-carboxylic acid **2** by L-phenylalanine methyl ester[a]



(*R*, *S*)-**4**
(*S*, *S*)-**4**

Entry	DCC / HOBt (equiv)	T (°C)	t (h)	Yield (%)[b] (*anti* + *syn*)
1	1.1 / 1.1	rt	16	24 + 25
2	4.0 / 0.2	rt	4	25 + 26
3	4.0 / 0	rt	24	< 10
4	1.2 / 0.2	rt	6	32 + 33
5	1.2 / 0.2	0 °C to rt	8	33 + 36
6	1.2 / 0.2	0 °C to rt	10	45 + 49[c]

[a] Boc-Protected **2** (200 mg, 0.65 mmol), DCC, HOBt in dichloromethane were allowed to stir at ambient temperature for 1 h followed by the addition of L-phenylalanine methyl ester and Et_3N (1.2 equiv).
[b] Isolated yield.
[c] Boc-Protected **2**, L-phenylalanine methyl ester, HOBt, Et_3N (1.2 equiv) in dichloromethane at 0 °C followed by the addition of EDC.

assignment (Fig. 1). Five amino acid derivatives were studied and, except for L-histidine methyl ester, the other four

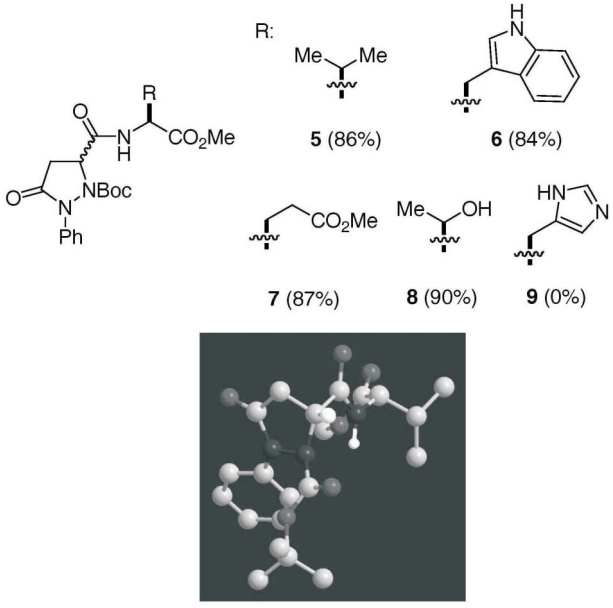
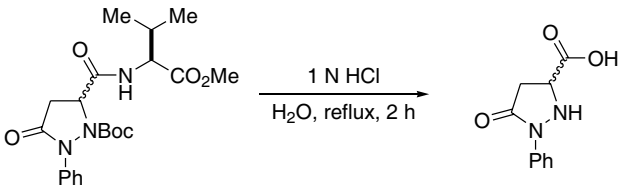


Fig. 1. Chemical structures of the diastereomers of compounds **5**-**9** and the stereoview of the Chem3D structure of (*R*,*S*)-**5** (regenerated from X-ray crystal coordinates).

desired adducts were obtained with high chemical yields (84~90%) in a roughly 1:1 ratio. Among the five diastereomeric pairs of products, only L-phenylalanine and L-valine methyl ester derivatives can be easily separated by flash column chromatography (hexanes/EtOAc). Fortunately, the easy crystallization of L-valine methyl ester derived (*R*)-5-oxo-1-phenyl-pyrazolidine-3-carboxylic acid ((*R,S*)-**5**) from CH_2Cl_2/hexanes allowed the assignment of absolute stereochemistry of both the diastereomers.

With the optical pure L-valine methyl ester derived (*R*)- and (*S*)-5-oxo-1-phenyl-pyrazolidine-3-carboxylic acid in hand, we then removed the resolving agent and Boc protecting group under acidic conditions. Treatment of (*R*,*S*)-**5** with 1 N HCl in refluxing H_2O for 2 h afforded the enantiomeric pure (+)-(*R*)-**2** ($[\alpha]_D^{20}$ +50.0 (*c* 0.5, MeOH)) with 94% yield (Scheme II). The antipode product (-)-(*S*)-**2** ($[\alpha]_D^{20}$ -48.6 (*c* 0.5, MeOH)) was obtained in 95% yield when (*S*,*S*)-**5** was used under the same reaction conditions.

Scheme II The acidic hydrolysis and deprotection of diastereomer (*R*,*S*)-**5** and (*S,S*)-**5**



(*R, S*)-**5**
(*S, S*)-**5**

(+)-(*R*)-**2** : (94%)
(-)-(*S*)-**2** : (95%)

In summary, we have developed an efficient method for the first optical resolution of (+)-(*R*)- and (-)-(*S*)-5-oxo-1-phenyl-pyrazolidine-3-carboxylic acid **2**. High overall yield (58% yield) of the resolved products were obtained and the process can be carried out with gram quantities. The optical pure enantiomer of (+)-(*R*)-**2** and (-)-(*S*)-**2** possesses a unique pyrazolidine structure and can be used as an organocatalyst in asymmetric reactions. The studies of organocatalysis using (+)-(*R*)-**2** and (-)-(*S*)-**2** for various organic reactions are actively underway in our group.

EXPERIMENTAL

General Methods

All reagents were used as purchased from commercial suppliers without further purification. NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer (400 MHz for ^{1}H, and 100 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal TMS standard for ^{1}H NMR and chloroform-*d* (δ 77.0) for ^{13}C NMR. Optical rotations were measured on a JASCO P-1010 polarimeter. EI mass spectra were recorded on a Finnigan TSQ-700 instrument at an ionizing energy of 70 eV and HRMS spectra were recorded on a JEOL SX-102A. Routine monitoring of reactions was performed using silica gel, glass-backed TLC plates (Merck Kieselgel 60 F254) and visualized by UV light (254 nm). Solvents were evaporated to dryness under reduced pressure using a rotary evaporator and the residue was purified by flash column chromatography on silica gel (230-400 mesh) with the indicated eluents. Air and/or moisture sensitive reactions were performed under inert atmosphere conditions.

Preparation of racemic 2

A mixture of maleic acid (5.0 g, 43.07 mmol) and phenylhydrazine (6.4 mL, 64.60 mmol) in water (50 mL) was stirred under refluxing conditions for 8 h. The mixture was cooled down to ambient temperature; at that time the precipitate which appeared was filtered off. The aqueous filtrate was extracted with CH_2Cl_2 (20 mL) and the layers were separated. The aqueous layer was acidified to pH = 0 ~ 2 with 1 N HCl, and then extracted with EtOAc (30 mL × 5). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was washed with $CHCl_3$ (20 mL × 5) to afford racemic **2** (6.39 g, 72%) as a white solid.

Preparation of racemic methyl 5-oxo-1-phenylpyrazolidine-3-carboxylate 3

To a solution of the racemic compound **2** (0.5 g, 2.43 mmol) was added 5% H_2SO_4 in MeOH (20.0 mL) dropwise and the mixture was brought to refluxing conditions for 3 h. The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (40 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using hexanes/EtOAc (2/1) as eluent to give white solid of **3** (0.35 g, 65%). IR ($CHCl_3$) ν 3648, 2958, 1741, 1700, 1597, 1498, 1235 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2H, *J* = 8.04 Hz), 7.35 (t, 2H, *J* = 8.04 Hz), 7.13 (t, 1H, *J* = 7.36 Hz), 5.28 (d, 1H, *J* = 9.68 Hz), 4.36 (dd, 1H, *J* = 18.40, 9.68 Hz), 3.82 (s, 3H), 2.97 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.27, 168.40, 138.27, 128.80, 124.74, 118.54, 55.32, 52.96, 37.92. HRMS *m/z* 220.0849 (calcd for

$C_{11}H_{12}N_2O_3$: 220.0848). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.03; H, 5.58; N, 12.71. Crystal data for **3** at 200 K: $C_{11}H_{12}N_2O_3$, M 220.23, Triclinic, P_{-1}, a = 6.7266(2) Å, b = 8.2764(3) Å, c = 10.3861(4) Å, V = 522.56(3) Å^3, Z = 2, λ = 0.71073 Å, D_c = 1.400 Mg/m^3, μ = 0.104 mm^{-1}, 6960 reflections, 146 parameters, R = 0.0763, R_w = 0.1953 for all data.

General procedure of the optical resolution for the preparation of a diastereomeric pair of products

To a solution of racemic **2** (135.0 mg, 0.66 mmol) in MeCN (15 mL) was added Boc_2O (0.17 mL, 0.79 mmol) and Et_3N (0.10 mL, 0.72 mmol) dropwise at ambient temperature. The mixture was allowed to stir for 2 h and was diluted with H_2O (20 mL) and extracted with EtOAc (40 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the Boc-protected crude product.

To a solution of the crude Boc-protected product (200 mg, 0.65 mmol) in dry CH_2Cl_2 (4 mL) was added L-phenylalanine methyl ester · HCl (169.1 mg, 0.78 mmol) and HOBt (17.7 mg, 0.13 mmol) at 0 °C. After the addition of Et_3N (0.12 mL, 0.85 mmol) and EDC (150.3 mg, 0.78 mmol), the mixture was allowed to warm up to ambient temperature for 10 h. The mixture was diluted with CH_2Cl_2 (10 mL) and H_2O was added (10 mL). The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude products were purified by flash column chromatography on silica gel using hexanes/EtOAc (6/1) as eluent to afford the corresponding pairs of diastereomer **4**.

(*R*)-*tert*-butyl-5-((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbamoyl)-3-oxo-2-phenylpyrazolidine-1-carboxylate (*R*,*S*)-**4**: mp. 127.5-128.5 °C. IR ($CHCl_3$) ν 3414, 1719, 1654, 1497, 1153 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.21 (m, 8H), 7.16-7.09 (m, 3H), 5.00 (dd, 1H, J = 11.52, 2.24 Hz), 4.92 (dt, 1H, J = 8.56, 5.40 Hz), 3.55 (s, 3H), 3.24-3.08 (m, 4H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.98, 168.32, 167.60, 156.03, 138.20, 135.37, 129.34, 128.66, 128.55, 127.27, 125.21, 119.67, 84.57, 59.22, 52.95, 52.22, 37.75, 33.82, 27.63. HRMS *m/z* 467.2059 (calcd for $C_{25}H_{29}N_3O_6$: 467.2056). Anal. Calcd for $C_{25}H_{29}N_3O_6$: C, 64.23; H, 6.25; N, 8.99. Found: C, 64.12; H, 6.20; N, 8.90.

(*S*)-*tert*-butyl-5-((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbamoyl)-3-oxo-2-phenylpyrazolidine-1-carboxylate (*S*,*S*)-**4**: mp. 117.5-118.2 °C. IR ($CHCl_3$) ν 3406, 1720, 1689, 1597, 1496, 1154 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4-7.2 (m, 5H), 7.11 (t, 1H, J = 7.12 Hz), 7.09-6.95 (m, 3H), 6.88 (d, 2H, J = 6.68 Hz), 4.97 (dd, 1H, J = 8.52, 2.92 Hz), 4.84 (q, 1H, J = 6.24 Hz), 3.77 (s, 3H), 3.25 (dd, 1H, J = 13.92, 5.12 Hz), 3.18-3.05 (m, 2H), 3.00 (dd, 1H, J = 13.92, 6.36 Hz), 1.25 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.55, 168.61, 167.63, 156.00, 138.45, 135.08, 128.88, 128.66, 128.53, 127.02, 125.09, 119.24, 84.64, 59.14, 53.65, 52.56, 37.44, 34.36, 27.67. HRMS *m/z* 467.2059 (calcd for $C_{25}H_{29}N_3O_6$: 467.2056). Anal. Calcd for $C_{25}H_{29}N_3O_6$: C, 64.23; H, 6.25; N, 8.99. Found: C, 64.12; H, 6.20; N, 8.90.

(*R*)-*tert*-butyl-5-((*S*)-1-methoxy-3-methyl-1-oxobutan-2-ylcarbamoyl)-3-oxo-2-phenylpyrazolidine-1-carboxylate (*R*,*S*)-**5**: mp. 122.8-124.2 °C. IR ($CHCl_3$) ν 3426, 2967, 1752, 1724, 1637, 1436, 1228 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 2H, J = 8.40 Hz), 7.38 (dd, 2H, J = 8.40, 7.64 Hz), 7.30 (d, 1H, J = 4.24 Hz), 7.18 (t, 1H, J = 7.64 Hz), 5.05 (dd, 1H, J = 10.00, 1.88 Hz), 4.58 (dd, 1H, J = 8.96, 4.24 Hz), 3.67 (s, 3H), 3.30 (dd, 1H, J = 17.36, 1.80 Hz), 3.15 (dd, 1H, J = 17.36, 10.00 Hz), 2.30-2.20 (m, 1H), 1.35 (s, 9H), 1.00 (d, 3H, J = 6.88 Hz), 0.97 (d, 3H, J = 6.92 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.67, 168.64, 167.86, 156.21, 138.37, 128.68, 125.54, 120.24, 84.67, 59.04, 57.38, 52.18, 33.40, 31.45, 27.70, 18.88, 17.63. HRMS *m/z* 419.2065 (calcd for $C_{21}H_{29}N_3O_6$: 419.2056). Anal. Calcd for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 59.81; H, 6.95; N, 9.90. Crystal data for (*R*,*S*)-**5** at 200 K: $C_{21}H_{29}N_3O_6$, M 419.47, Monoclinic, $P2_1$, a = 6.3290(2) Å, b = 14.4830(5) Å, c = 12.3790(5) Å, V = 1100.95(7) Å^3, Z = 2, λ = 0.71073 Å, D_c = 1.265 Mg/m^3, μ = 0.093 mm^{-1}, 6696 reflections, 272 parameters, R = 0.0660, R_w = 0.1486 for all data.

(*S*)-*tert*-butyl-5-((*S*)-1-methoxy-3-methyl-1-oxobutan-2-ylcarbamoyl)-3-oxo-2-phenylpyrazolidine-1-carboxylate (*S*,*S*)-**5**: mp. 104.7-106.5 °C. IR ($CHCl_3$) ν 3320, 2975, 1730, 1701, 1682, 1597, 1500, 1153 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2H, J = 7.80 Hz), 7.37 (t, 2H, J = 7.80 Hz), 7.22 (d, 1H, J = 8.60 Hz), 7.16 (t, 1H, J = 7.44 Hz), 5.06 (dd, 1H, J = 6.92, 4.56 Hz), 4.57 (dd, 1H, J = 8.60, 4.64 Hz), 3.77 (s, 3H), 3.19 (s, 1H), 3.18 (d, 1H, J = 2.44 Hz), 2.18-2.07 (m, 1H), 1.35 (s, 9H), 0.79 (d, 3H, J = 6.84 Hz), 0.74 (d, 3H, J = 6.92 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.89, 168.69, 168.24, 156.08, 138.69, 128.82, 125.24, 118.79, 84.86, 59.63, 57.36, 52.30, 34.64, 31.21, 27.75, 18.67, 17.42. HRMS *m/z* 419.2065 (calcd for

$C_{21}H_{29}N_3O_6$: 419.2056).

(*R*)- and (*S*)-*tert*-butyl-5-((*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-ylcarbamoyl)-3-oxo-2-phenyl-pyrazolidine-1-carboxylate **6**: An inseperable mixture of diastereomers. Selected peaks of the diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.64 (s, 1H), 7.58 (d, 1H, *J* = 7.80 Hz), 7.38 (t, 3H, *J* = 7.44 Hz), 7.32 (d, 1H, *J* = 8.60 Hz), 7.25-6.90 (m, 15H), 6.54 (d, 1H, *J* = 2.20 Hz), 5.10-4.80 (m, 4H), 3.75 (s, 3H), 3.48-3.03 (m, 11H), 1.80 (s, 1H), 1.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.99, 171.51, 168.65, 168.46, 167.88, 167.84, 156.20, 155.95, 138.32, 138.18, 136.23, 136.04, 128.67, 128.53, 127.54, 127.01, 125.23, 125.12, 123.26, 123.21, 122.39, 121.99, 120.01, 119.46, 119.43, 119.34, 118.56, 118.06, 111.38, 109.53, 108.69, 84.79, 84.60, 59.57, 59.52, 53.15, 52.98, 52.72, 52.29, 34.76, 34.26, 27.71, 27.67, 27.48, 27.24. HRMS *m/z* 506.2159 (calcd for $C_{27}H_{30}N_4O_6$: 506.2165).

(*R*)- and (*S*)-*tert*-butyl 5-((*S*)-1,3-di(methoxycarbonyl)-propylcarbamoyl)-3-oxo-2-phenylpyrazolidine-1-carboxylate **7**: An inseperable mixture of diastereomers. Selected peaks of the diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.45 (m, 6H), 7.42-7.33 (m, 4H), 7.16 (td, 2H, *J* = 7.40, 3.44 Hz), 5.07-5.01 (m, 2H), 4.70-4.58 (m, 2H), 3.79 (s, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 3.60 (s, 3H), 3.30-3.09 (m, 4H), 2.53-1.92 (m, 8H), 1.35 (s, 9H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.17, 172.93, 171.74, 171.55, 168.91, 168.15, 167.84, 156.32, 156.11, 138.68, 138.48, 128.79, 128.66, 125.44, 125.28, 120.06, 119.13, 84.77, 84.74, 59.39, 59.15, 52.69, 52.60, 51.98, 51.95, 51.91, 51.79, 34.28, 33.70, 29.95, 29.46, 27.73, 27.72, 27.22, 26.93. HRMS *m/z* 463.1961 (calcd for $C_{22}H_{29}N_3O_8$: 463.1955).

(*R*)- and (*S*)-*tert*-butyl 5-((*2S*,*3R*)-3-hydroxy-1-methoxy-1-oxobutan-2-ylcarbamoyl)-3-oxo-2-phenyl-pyrazolidine-1-carboxylate **8**: An inseperable mixture of diastereomers. Selected peaks of the diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (t, 4H, *J* = 7.64 Hz), 7.48 (t, 2H, *J* = 10.48 Hz), 7.37 (m, 4H), 7.17 (q, 2H, *J* = 7.12 Hz), 5.12 (m, 2H), 4.62 (dd, 1H, *J* = 9.08, 1.88 Hz), 4.57 (dd, 1H, *J* = 8.96, 1.76 Hz), 4.42 (m, 2H), 3.78 (s, 3H), 3.60 (s, 3H), 3.20 (m, 4H), 2.62 (s, 1H, OH), 2.32 (s, 1H, OH), 1.33 (s, 9H), 1.31 (s, 9H), 1.25 (d, 3H, *J* = 6.40 Hz), 1.01 (d, 3H, *J* = 6.40 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.78, 170.65, 169.44, 169.37, 168.17, 167.90, 156.12, 155.97, 138.42, 138.33, 128.70, 128.60, 125.44, 125.30, 120.07, 119.27, 84.77, 84.74, 67.80, 67.50, 59.55, 59.10, 57.50, 57.32, 52.63, 52.51, 34.49, 33.79, 27.66, 19.92, 19.82. HRMS *m/z* 421.1847 (calcd for $C_{20}H_{27}N_3O_7$: 421.1849).

Preparation of (+)-(*R*)- and (-)-(*S*)-5-oxo-1-phenyl-pyrazolidine-3-carboxylic acid 2

To a solution of diastereomer (*R*,*S*)-**5** (0.5 g, 1.07 mmol) was added 1 N HCl (10 mL) and the reaction was brought to reflux for 2 h. The mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude products were washed with $CHCl_3$ (10 mL × 2), afforded (+)-(*R*)-**2** as a white solid (207.4 mg, 94%; $[\alpha]_D^{20}$ +50.0 (*c* 0.5, MeOH)). Diastereomer (*S*,*S*)-**5** (0.5 g, 1.07 mmol) was used under the same conditions to afforded the white solid of (-)-(*S*)-**2** (209.6 mg, 95%; $[\alpha]_D^{20}$ -48.6 (*c* 0.5, MeOH)). mp. 217.2-218.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, 2H, *J* = 8.08 Hz), 7.36 (t, 2H, *J* = 8.08 Hz), 7.10 (t, 1H, *J* = 7.34 Hz), 4.27 (dd, 1H, *J* = 8.44, 5.96 Hz), 3.00 (dd, 1H, *J* = 16.44, 8.44 Hz), 2.79 (dd, 1H, *J* = 16.44, 5.96 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.81, 170.54, 139.48, 128.96, 124.10, 118.40, 55.37, 37.78. HRMS *m/z* 206.0695 (calcd for $C_{10}H_{10}N_2O_3$: 206.0691).

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