A Convenient Approach to the Synthesis of \( \omega \)-Heterocyclic Amino Acids from Carboxy Lactams through Ring–Chain Transformation; Part 1: Synthesis of (2\( S \))-/(2\( R \))-2-Amino-4-(1-aryl-/1,5-diaryl-1\( H \)-pyrazol-3-yl)butyric Acid

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Abstract: A general method is reported for the synthesis of \( \omega \)-heterocyclic \( \alpha \)-amino acids, which involves preparation of enaminone intermediates from thiolactams, followed by reaction with dinucleophiles, resulting in a single-step condensation and ring–chain transformation to the desired \( \omega \)-heterocyclic \( \alpha \)-amino acids after deprotection of amine and carboxylic group. The reaction steps preserve the chirality of the parent-substituted lactam. The method is illustrated by the synthesis of (2\( S \))- and (2\( R \))-2-amino-4-(1-aryl-/1,5-diaryl-1\( H \)-pyrazol-3-yl)butyric acids.

Key words: amino acids, ring opening, chirality, lactams, hydroge-
nations

Unnatural amino acids, particularly \( \alpha \)-amino acids, have enriched medicinal chemistry research in many ways. They have been used\(^2\) extensively in peptide analoguing to modify conformational flexibility, to enhance enzymatic stability and to improve pharmacodynamic and bioavailability characteristics of medicinally important peptides. Numerous therapeutically important compounds with an unnatural amino acid moiety in their structures have been reported.\(^3\)\-\(^7\) Current developments in genomics and proteomics hold promise of providing a myriad of virgin new protein targets whose actions will be open for modulation by small molecules. Unnatural amino acids have the potential of providing structurally and functionally unique chemo-types to cater to both small molecule needs and related peptides for drug research. As a consequence, the development of versatile new methodology for the preparation of proteinogenic, natural, and unnatural amino acids in optically pure form has emerged as a highly significant and challenging synthetic endeavor.

Many reviews describing synthesis and applications of unnatural \( \alpha \)-amino acids are available.\(^3\) The main objective of the present study was to design novel analogs of natural amino acids carrying modified electronic interaction sites in the side chain which could influence interactions with the receptors/acceptor molecules and may further elucidate biological recognition. A short path synthesis is described in this paper, which is unique in its versatility to afford optically active unnatural \( \alpha \)-amino acids and its higher analogs, simply by extending the lactam ring size.

Lactams have been the subject of much study in our laboratory\(^8\) to explore the scope that lactams and their activated forms offer for generating molecular diversity due to their ability to undergo facile nucleophilic, electrophilic and cycloaddition reactions. Lactams also provide easy access to reactive species such as enaminones (1, \( X = \text{CH} \)), and theiraza analogues (1, \( X = \text{N} \)), which are useful intermediates for building aromatic, carboxylic and heterocyclic rings on the azacycloalkane platform (Path A), and for ready entry to side chain \( \omega \)-functionalized alkyl heterocycles by ring-chain transformation reaction (Path B).\(^8\) The path B transformation seemed to provide a useful core reaction strategy for the synthesis of \( \omega \)-substituted \( \alpha \)-amino acids with much possibility for introduction of structural variations and creation of molecular diversity (Figure 1). This strategy has been used successfully for the development of methods for the synthesis of optically active \( \omega \)-heterocyclic-\( \alpha \)-amino acids.

**Figure 1**

The starting methyl L-thiopyroglutamate 4 was prepared from L-glutamic acid following the procedure described in the literature.\(^9\) The thiolactam 4 was subjected to sulfur extrusion reaction by following the literature procedure\(^10\) to afford enaminones 5\( a \)-\( c \) in fair yields depending upon the electrophile chosen (Scheme 1, Table 1). The enaminones 5\( a \) exhibited the required spectral and analytical profiles.

Enaminones 5\( a \) were then subjected to regiospecific ring-chain transformation\(^11\) by reactions with hydroxylamine, hydrazide and phenylhydrazine in protic solvents like MeOH or EtOH at reflux for a period of 12–36 hours to afford the desired (2\( S \))-\( (S) \)-2-benzylamino-4-(5-aryl-isox-
azol-3-yl)butyric acid methyl ester 6a,b and (2S)-(+) -2-benzylamino-4-(5-aryl-1-(un)substituted-1H-pyrazol-3-yl)butyric acid methyl ester 7a–e in 78–94% yields (Scheme 2, Table 1). The structure of products 6 and 7 was confirmed by spectroscopic methods (see experimental section). The differentiation between the isomeric structures of 7c–e is possible by 1H NMR (ArH signals are shifted downfield) and 13C NMR (γ-CH₂ and 3-C₃pyr signals downfield shifted) and such observations have been reported earlier.11

Scheme 1

With 1-arylpyrazolyl amino acid esters 7c–e, N-debenzylation occurred easily in cyclohexene12 in the presence of Pd-C as catalyst to give (2S)-(+) -2-amino-4-(1,5-aryl-1H-pyrazol-3-yl)butyric acid methyl ester 8b–d, whereas with (2S)-(+) -2-benzylamino-4-(5-aryl-1H-pyrazol-3-yl)butyric acid methyl ester 7a, N-debenzylation was easiest in formic acid and Pd-C to afford (2S)-(+) -2-amino-4-(5-aryl-1H-pyrazol-3-yl)butyric acid methyl ester 8a in good yield (Scheme 3, Table 1). However, other catalytic transfer hydrogenation conditions and classical catalytic hydrogenation did not deprotect nitrogen so cleanly. N-Debenzylation of (2S)-(+) -2-benzylamino-4-(5-aryl-isoxazol-3-yl)butyric acid methyl esters 6a,b could not be achieved successfully as isoxazolyl rings underwent fission under various experimental conditions attempted. Development of experimental conditions to circumvent this problem is under study and will form part of future reports. The acidic hydrolysis of the esters 8a–d afforded the desired (2S)-(+) -2-amino-4-[5-aryl-1-(un)substituted-1H-pyrazol-3-yl]butyric acids 9a–d in good yields, which were isolated as hydrochloride salts (Scheme 3, Table 2).

Following a similar sequence of reactions, methyl D-thiopyroglutamate 10 was converted to (2R)-(−)-2-amino-4-

Table 1 Physical Data of Various Synthesized Intermediates

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
<th>Optical rotation&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>33</td>
<td>Oil</td>
<td>+144.1</td>
</tr>
<tr>
<td>5b</td>
<td>48</td>
<td>101–102</td>
<td>+187.2</td>
</tr>
<tr>
<td>5c</td>
<td>23</td>
<td>78–79</td>
<td>+245</td>
</tr>
<tr>
<td>6a</td>
<td>59</td>
<td>63–64</td>
<td>+246</td>
</tr>
<tr>
<td>6b</td>
<td>79</td>
<td>Oil</td>
<td>+10.3</td>
</tr>
<tr>
<td>7a</td>
<td>78</td>
<td>Oil</td>
<td>+19.3</td>
</tr>
<tr>
<td>7b</td>
<td>94</td>
<td>Oil</td>
<td>+14.3</td>
</tr>
<tr>
<td>7c</td>
<td>93</td>
<td>Oil</td>
<td>+15.3</td>
</tr>
<tr>
<td>7d</td>
<td>87</td>
<td>Oil</td>
<td>+1.5</td>
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<tr>
<td>7e</td>
<td>83</td>
<td>Oil</td>
<td>+14.5</td>
</tr>
<tr>
<td>8a</td>
<td>78</td>
<td>157–159</td>
<td>+25.0</td>
</tr>
<tr>
<td>8b</td>
<td>79</td>
<td>120–121</td>
<td>+21.1</td>
</tr>
<tr>
<td>8c</td>
<td>82</td>
<td>133–134</td>
<td>+20.9</td>
</tr>
<tr>
<td>8d</td>
<td>93</td>
<td>128–129</td>
<td>+33.9</td>
</tr>
<tr>
<td>11a</td>
<td>74</td>
<td>Oil</td>
<td>−141</td>
</tr>
<tr>
<td>11b</td>
<td>76</td>
<td>92–93</td>
<td>−198</td>
</tr>
<tr>
<td>11c</td>
<td>65</td>
<td>79–80</td>
<td>−211</td>
</tr>
<tr>
<td>12</td>
<td>89</td>
<td>154–155</td>
<td>−27.0</td>
</tr>
<tr>
<td>13</td>
<td>97</td>
<td>Oil</td>
<td>−23.0</td>
</tr>
<tr>
<td>14</td>
<td>83</td>
<td>160–161</td>
<td>−22.7</td>
</tr>
</tbody>
</table>

<sup>a</sup> For spectroscopic and analytical data, see the experimental section.

<sup>b</sup> Yields of analytically pure products.

<sup>c</sup> For concentration of compound and solvent used, see the experimental section.
(5-phenyl-1H-pyrazol-3-yl)butyric acid (15) as shown in Scheme 4 (Table 2). The compounds 9a-d and 15 were fully characterized on the basis of complementary spectroscopic (1H NMR and MS) and analytical data. The preservation of the chirality in each reaction sequence of the synthesis was established by comparing specific optical rotation \([\alpha]_D^{24}\) of each intermediate product with their antipodes. Finally the enantiomeric excesses was established by chiral HPLC analysis and it was found to be > 98% ee.

The successful exploration of methyl L- and D-thiopyrroglutamate as synthons for the generation of novel \(\alpha\)-heterocyclic \(\alpha\)-amino acids have been achieved to pave the way for synthesis of close analogues of a proteinogenic amino acids such as histidine. The same methodology can be employed in the synthesis of unnatural \(\beta\)- and \(\gamma\)-amino acids and even its higher analogues simply by extending the lactam ring size, and varying the position of carboxyl group on the lactam ring on which we are presently working in our laboratory.

Scheme 4: Reagents and conditions: (i) Ac2O, Br, Ph,P, Et,N, MeCN–CH2Cl2, r.t., 24 h; (ii) H2NOH, MeOH or EtOH, reflux, 10 h; (iii) NH2NH2, MeOH or EtOH, reflux, 12 h; (iv) HCOOH, 10% Pd–C, reflux, 8 h; (v) 6 N HCl, reflux 6 h.

Table 2: Physical Data of Unnatural \(\alpha\)-Amino Acids Synthesized

<table>
<thead>
<tr>
<th>Compound(\text{a})</th>
<th>Yield (%)*</th>
<th>Melting Point °C</th>
<th>Optical rotation(\text{b}) ([\alpha]_D^{24})</th>
<th>Purity (% ee)*d</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>88</td>
<td>240–241</td>
<td>34.8</td>
<td>99.1</td>
</tr>
<tr>
<td>9b</td>
<td>96</td>
<td>215–216</td>
<td>4.1</td>
<td>98.7</td>
</tr>
<tr>
<td>9c</td>
<td>90</td>
<td>190–191</td>
<td>11.5</td>
<td>98.1</td>
</tr>
<tr>
<td>9d</td>
<td>97</td>
<td>118–119</td>
<td>19.9</td>
<td>98.5</td>
</tr>
<tr>
<td>15</td>
<td>90</td>
<td>234–235</td>
<td>–32.9</td>
<td>98.9</td>
</tr>
</tbody>
</table>

\(\text{a}\) For spectroscopic and analytical data, see the experimental section.

\(\text{b}\) Yields of analytically pure products.

\(\text{c}\) For concentration of compound and solvent used, see the experimental section.

\(\text{d}\) Determined by chiral HPLC analysis using Kromasil C18 column.

150 mm) analytical column. The compounds were eluted at a flow rate of 1.5 mL/min and detected at 240 nm, using pH 4.5 buffer–MeOH (70:30) as eluent. The chiral purity and enantiomeric excesses of the amino acids were determined by chiral HPLC analysis using Chiraldex (5 \(\mu\), 4.6 \(\times\) 25 mm) column. The compounds were eluted at flow rate of 0.5 mL/min and detected at 220 nm, using pH 3.0 buffer–MeCN (30:70) as eluent. Elemental analyses were carried out with a Perkin Elmer 2400 analyzer and values found were within 1.0% of theoretical values.

(S)-(+) 1-Benzyl-5-(2-oxo-2-phenylthiophenyl)pyrrolidine-2-carboxylic Acid Methyl Ester (5a): Typical Procedure

To a solution of thiolactam 4 (24.9 g, 100 mmol) in anhyd MeCN (48 mL), phenacyl bromide (24.9 g, 125 mmol) was added and the reaction mixture was stirred for 8 h at r.t. The solid, which separated out, was dissolved by addition of anhyd CH2Cl2 (500 mL) and stirred for 0.5 h at the same temperature. Ph,P (39.3 g, 150 mmol) and Et,N (30.3 g, 300 mmol) were then added one after another, and the reaction mixture was stirred for another 24 h at the same temperature. Solvents were removed under reduced pressure and the residue was dissolved in EtOAc (500 mL), washed with H2O (3 \(\times\) 100 mL), brine (1 \(\times\) 100 mL), dried (Na2SO4) and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by column chromatography over silica gel (100–200 mesh) using EtOAc–hexanes (2:8) as eluent to give 5a as a colorless thick oil; yield: 11.0 g (33%); \([\alpha]_D^{24} +144.1\) (c = 1, MeOH).

IR (CH2Cl2): 1742, 1695 cm\(^{-1}\).

1H NMR (300 MHz, CDCl3); \(\delta = 2.00–2.03\) (m, 4 H), 3.34 (q, \(J = 9.2\) Hz, 1 H), 3.69 (s, 3 H), 4.35 (d, \(J = 15.0\) Hz, 1 H), 4.75 (d, \(J = 15.1\) Hz, 1 H), 5.98 (s, 1 H), 7.19–7.81 (m, 10 H).

MS: \(m/z\) = 336 [M + 1].

Anal. Calcd for C21H21NO3: C, 75.38; H, 6.53; N, 4.18. Found: C, 75.38; H, 6.53; N, 4.29.

(S)-(+) 1-Benzyl-5-(2-oxo-2-phenylethylidene)pyrrolidine-2-carboxylic Acid Methyl Ester (5b)

Isolated as a white solid in 48% yield; mp 101–102 °C; \([\alpha]_D^{24} +19.9\) (c = 1, MeOH).

IR (CH2Cl2): 1742, 1695 cm\(^{-1}\).

1H NMR (300 MHz, CDCl3); \(\delta = 2.00–2.03\) (m, 4 H), 3.34 (q, \(J = 9.2\) Hz, 1 H), 3.69 (s, 3 H), 4.35 (d, \(J = 15.0\) Hz, 1 H), 4.75 (d, \(J = 15.1\) Hz, 1 H), 5.98 (s, 1 H), 7.19–7.81 (m, 10 H).

MS: \(m/z\) = 336 [M + 1].

Anal. Calcd for C21H21NO3: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.38; H, 6.53; N, 4.29.

Melting points were recorded on a Büchi B-540 melting point apparatus. Compounds were routinely checked for their purity on silica gel 60 F254 TLC plates and their spots were visualized by exposing them to iodine vapor, UV lamp or by spraying the plates with Dragendorff’s or ninhydrine or KMnO4 reagents. IR spectra (\(\lambda_{\text{max}}\) in cm\(^{-1}\)) were recorded on Perkin Elmer Paragon-1000 PC instrument and NMR (300 MHz) spectra were recorded on Bruker 300-DRX spectrometer as solutions using TMS as internal standard, and chemical shifts are expressed in \(\delta\) units. Mass spectra were recorded on API-3000 LC-MS/MS instrument using direct inlet system under positive ion electrospray ionization source and GC-MS spectra were recorded on Finnigan NAT-GCQ instrument. Optical rotations were taken on Autopol-III instrument. The purity of final products was determined by HPLC analysis on Kromasil (C18, 5 μL, 4.6×
(S)-(++)-1-Benzyl-5-[2-(4-methoxyphenyl)-2-oxoethylidene]pyrrolidine-2-carboxylic Acid Methyl Ester (5c)

Isolated as a white solid in 23% yield; mp 78–79 °C; [α]D24 = +24.6 (c = 0.5, MeOH).

IR (KBr): 1748, 1573, 1451, 1223 cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 1.99–2.20 (m, 2 H), 2.25 (br s, 1 H), 2.90 (dd, J = 3.0, 9.0 Hz, 2 H), 3.39 (dd, J = 3.0, 6.0 Hz, 1 H), 4.63 (d, J = 14.0 Hz, 1 H), 3.69 (d, J = 14.0 Hz, 1 H), 3.76 (s, 3 H), 3.90 (d, J = 14.0 Hz, 1 H), 6.28 (s, 1 H), 7.16–7.22 (2 H) 7.26–7.38 (m, 5 H), 7.43–7.50 (m, 3 H), 7.74–7.77 (m, 2 H).

MS: m/z = 351 [M + 1].


(S)-(++)-2-Benzylamino-4-[5-(4-fluorophenyl)isoxazol-3-yl]butyric Acid Methyl Ester (6b)

Isolated as a thick oil in 74% yield; [α]D24 = +10.3 (c = 1, MeOH).

IR (CHCl3): 3419, 2909, 1739, 1617, 1510 cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 1.97–2.11 (m, 2 H), 2.15 (br s, 1 H), 3.68 (s, 1 H), 4.63 (d, J = 14.0 Hz, 1 H), 7.20 (d, J = 6.5 Hz, 2 H), 7.21–7.34 (m, 4 H), 7.70 (d, J = 6.5 Hz, 2 H).

MS: m/z = 370 [M + 1].


(S)-(++)-2-Benzylamino-4-[5-(4-fluorophenyl)-1H-pyrazol-3-yl]butyric Acid Methyl Ester (7b)

Isolated as a thick oil in 93% yield; [α]D24 = +14.3 (c = 1, MeOH).

IR (CHCl3): 1707, 1570, 1464, 1201 cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 1.91–2.11 (m, 2 H), 2.15 (br s, 1 H), 2.84 (t, J = 7.0 Hz, 2 H), 3.33 (q, J = 6.0 Hz, 1 H), 3.66 (d, J = 14.0 Hz, 1 H), 3.74 (s, 3 H), 3.86 (d, J = 14.0 Hz, 1 H), 6.33 (s, 1 H), 7.20–7.43 (m, 8 H), 7.72 (d, J = 8.0 Hz, 2 H), 13.35 (br s, 1 H).

MS: m/z = 350 [M + 1].

Anal. Calcd for C21H22FNO3 (349.43): C, 72.18; H, 6.63; N, 12.03. Found: C, 71.95; H, 6.81; N, 11.86.

(S)-(++)-2-Benzylamino-4-[5-(4-fluorophenyl)-1H-pyrazol-3-yl]butyric Acid Methyl Ester (7c)

Isolated as a thick oil in 93% yield; [α]D24 = +14.53 (c = 0.076, MeOH).

IR (CHCl3): 3419, 2909, 1739, 1617, 1510 cm⁻¹.
\( \text{N-Debenzylation of 7 and 13; General Method} \)

**Method 1:** A mixture of N-benzyl amino acid esters 7 or 13 (1.0 g), 10% Pd-C (1.0 g), formic acid (50 mL) was refluxed with stirring for 4–12 h. After completion of reaction, reaction mixture was cooled to r.t. and filtered through Celite bed, washed with EtOH (2 \( \times \) 5 mL) and the combined filtrate was concentrated under reduced pressure to afford crude amino acid esters. These crude amino acid esters were purified by treating them with ethereal HCl, or their N-Boc derivative was prepared and purified by column chromatography over silica gel (200–400 mesh), which upon treatment with methanolic HCl afforded the pure amino acid ester as hydrochloride salt.

**N-Boc Protection; General Method**

To a stirred solution of crude amino acid ester (1 equiv) in CH\(_2\)Cl\(_2\) (20 mL) were added t-Boc anhydride (1.1 equiv) and Et\(_3\)N (1.1 equiv) at 0 °C. The resulting reaction mixture was stirred for 1–3 h at the same temperature. After completion of reaction, the mixture was diluted with CH\(_2\)Cl\(_2\) (50 mL) and washed with chilled 10% NaHCO\(_3\) (3 \( \times \) 50 mL), brine (1 \( \times \) 50 mL), dried (Na\(_2\)SO\(_4\)) and filtered. The filtrate was concentrated under reduced pressure to afford a crude product, which was purified by column chromatography over silica gel (100–200 mesh) using 0.5% MeOH–CHCl\(_3\) as eluent to afford the pure N-Boc derivative of amino acid ester.

**N-Boc Deprotection; General Method**

To a stirred solution of pure N-Boc amino acid ester in MeOH (5 mL) was added 1 M MeOH–HCl (5 equiv) at 0 °C and resulting re-action mixture stirred at the same temperature until TLC indicated complete disappearance of the starting material (10–12 h). Solvent was removed under reduced pressure to afford a solid material, which was dried under reduced pressure to afford the corresponding amino acid esters as HCl salts.

**Method 2:** A mixture of N-benzyl amino acid esters 7 or 13 (1.0 g), 10% Pd-C (0.5 g), cyclohexene (100 mL) was refluxed with stirring for 6–18 h. After completion of reaction, reaction mixture was cooled to r.t. and filtered through a Celite bed, washed with EtOH (2 \( \times \) 5 mL) and the filtrate was concentrated under reduced pressure to afford the crude amino acid esters which were purified as described above in Method 1.

\( \text{(S)-(+)2-Benzamino-4-[5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl]butyric Acid Methyl Ester (7a)} \)

Isolated as a white hydrochloride salt in 78% yield; mp 157–159 °C; \([\alpha]_D^{25} +25.0 (c = 0.95, \text{MeOH})\).

IR (KBr): 3434, 1720, 1629, 1456 cm\(^{-1}\).

\( \text{1H NMR (300 MHz, CDCl}_3\text{)}: \delta = 2.40–2.46 (m, 2 H), 2.87–2.94 (m, 2 H), 3.50 (br s, 1 H), 3.67 (d, \( J = 2.03\) Hz, 1 H), 3.72 (s, 6 H), 3.80 (s, 3 H), 3.86 (d, \( J = 14.0\) Hz, 1 H), 6.20 (s, 1 H), 6.79–6.84 (m, 2 H), 7.08–7.11 (m, 2 H), 7.28–7.37 (m, 10 H).

**Method 2:** A mixture of \( 7a \) (1.0 g), 10% Pd-C (0.5 g), cyclohexene (100 mL) was refluxed with stirring for 6–18 h. After completion of reaction, reaction mixture was cooled to r.t. and filtered through a Celite bed, washed with EtOH (2 \( \times \) 5 mL) and the filtrate was concentrated under reduced pressure to afford the crude amino acid esters which were purified as described above in Method 1.
(S)-(–)2-Amino-4-(5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)butyric Acid Methyl Ester (8e) (Method 2)
Isolated as an off-white hydrochloride salt from compound 7d in 82% yield; mp 133–134 °C; [α]D24 +20.9 (c = 0.098, MeOH).
IR (KBr): 3423, 2933, 1743, 1613, 1508, 1438 cm⁻¹.
1H NMR (300 MHz, D2O): δ = 2.26–2.30 (m, 2 H), 2.72–2.80 (m, 2 H), 3.36 (s, 3 H), 3.70 (s, 3 H), 4.21 (t, J = 6.5 Hz, 1 H), 6.28 (s, 1 H), 6.43–7.05 (m, 9 H).
MS: m/z = 366 [M + 1].
Anal. Calcd for C21H23N3O3·2HCl (438.35): C, 57.54; H, 5.75; N, 16.18. Found: C, 59.96; H, 6.70; N, 15.91.

(R)-(+)2-Amino-4-(5-(phenyl-1H-pyrazol-3-yl)butyric Acid Methyl Ester (14) (Method 1)
Isolated as a white hydrochloride salt from compound 7e in 93% yield; mp 128–129 °C; [α]D24 +33.9 (c = 1.5, MeOH).
IR (KBr): 3440, 1743, 1710, 1617, 1520, 1240 cm⁻¹.
1H NMR (300 MHz, D2O): δ = 2.23–2.34 (m, 2 H), 2.71–2.85 (m, 2 H), 3.32 (s, 3 H), 3.46 (s, 3 H), 3.67 (s, 3 H), 4.18 (t, J = 6.5 Hz, 1 H), 6.29 (s, 1 H), 6.41–6.44 (m, 2 H), 6.59–6.62 (m, 2 H), 6.68–6.92 (m, 4 H).
MS: m/z = 396 [M + 1].

Ester Hydrolysis of 8 and 14; General Method
A solution of amino acid esters 8 or 14 (1.0 g) in 6 N HCl (5 mL) was refluxed under stirring for 4–6 h and then evaporated. The residue was suspended in CHCl₃, and a 4 N CHCl₃–NH₄OH solution was added at 0 °C until the pH was neutral and the resulting reaction mixture was stirred at the same temperature for 10 min. The solid, which separated out, was filtered, washed with water and dried to afford the pure amino acid.

(S)-(+)2-Amino-4-(5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)butyric Acid (9a)
Isolated as an off-white solid in 88% yield; mp 240–241 °C; [α]D24 +11.5 (c = 1, MeOH); HPLC purity: 99.5%, and chiral purity: 98.1%.
IR (KBr): 3562, 1646, 1504, 1438 cm⁻¹.
1H NMR (300 MHz, D2O): δ = 2.90–2.96 (m, 2 H), 3.50–3.55 (m, 2 H), 4.03 (s, 3 H), 4.55 (s, 1 H), 7.08–7.15 (m, 3 H), 7.40–7.45 (m, 4 H), 7.60–7.80 (m, 3 H).
MS: m/z = 352 [M + 1].
Found: C, 57.29; H, 6.61; N, 12.10.

(S)-(+)2-Amino-4-(5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)butyric Acid (9d)
Isolated as an off-white solid in 97% yield; mp 118–119 °C; [α]D24 +32.9 (c = 1.6, MeOH); HPLC purity: 99.3%, and chiral purity: 98.5%.
IR (KBr): 3429, 1639, 1590, 1489, 1408 cm⁻¹.
1H NMR (300 MHz, D2O): δ = 2.50–2.20 (m, 2 H), 2.64–2.66 (m, 2 H), 3.19 (s, 3 H), 3.31 (s, 3 H), 3.93 (br s, 1 H), 6.11 (s, 1 H), 6.24–6.26 (m, 4 H), 6.70–6.73 (m, 4 H).
MS: m/z = 382 [M + 1].
Found: C, 65.89; H, 5.86; N, 11.27.

References
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(c) Pätzel, M.; Liesbcher, J. *Synthesis* 1995, 879; and references cited therein.