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A convenient and new approach to the synthesis of ω-heterocyclic amino acids from carboxy lactams through ring-chain-transformation. Part 2: Synthesis of (2*R*)-/(2*S*)-2-aminomethyl-3-(1-aryl-/1,5-diaryl-1*H*-pyrazol-3-yl)-propionic acid

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Abstract—Making use of amide activation, a convenient and short path synthesis of optically pure ω-heterocyclic-β-amino acids has been achieved from (1*R*,3*R*)- and (1*R*,3*S*)-5-oxo-1-(1-phenyl-ethyl)-pyrrolidine-3-carboxylic acid methyl ester. The key step of the synthesis involves a regiospecific ring-chain-transformation of the enaminones when subjected to 1,2-binucleophilic attacks. The method is illustrated by the synthesis of (2*R*)-/(2*S*)-2-aminomethyl-3-(1-aryl-/1,5-diaryl-1*H*-pyrazol-3-yl)-propionic acid.

1. Introduction

Unnatural amino acids[1–3] have stimulated much recent interest. Among unnatural amino acids, β-amino acids[4] has attracted much attention. Oligomeric β-amino acids form novel folded structures, which have shown to exhibit novel physicochemical and biological activities. They are being used as peptidomimetics and have emerged as an important class of building blocks in combinatorial library building and drug discovery. Moreover many of the developmental pharmaceuticals contain β-amino acids as critical components.[5]

We had earlier demonstrated the convenient synthesis of optically active ω-heterocyclic-α-amino acids.[6] The present study is aimed as an extension of this efficient methodology to the synthesis of optically active ω-heterocyclic-β-amino acid from activated lactams. This paper describes chiral syntheses of 2-aminomethyl-3-[1-(un)substituted-5-aryl-1*H*-pyrazol-3-yl]-propionic acids from optically active lactams derived from itaconic acid.

2. Results and discussion

With a view to establish the feasibility of this approach racemic 2-methylaminomethyl-3-[1-(un)substituted-5-aryl-1*H*-pyrazol-3-yl/5-aryl-isoxazol-3-yl]-propionic acid methyl esters **4** and **5** were first synthesized as model compounds. The compounds **4** and **5** were prepared as described in Scheme 1, starting from 1-methyl-5-oxopyrrolidine-3-carboxylic acid methyl ester (**1**), which in turn was prepared from itaconic acid according to the procedure described in literature.[7] The compound **1** was then treated with Lawesson's reagent to give the corresponding thiolactam **2** in quantitative yield. The sulfur extrusion reaction[6] on thiolactam **2** with various phenacyl bromide afforded 1-methyl-5-(2-aryl-2-oxo-ethylidene)-pyrrolidine-

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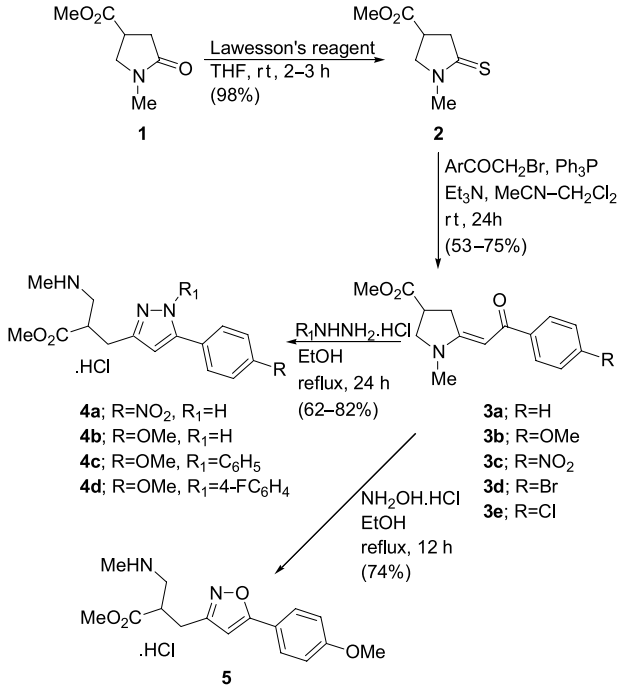
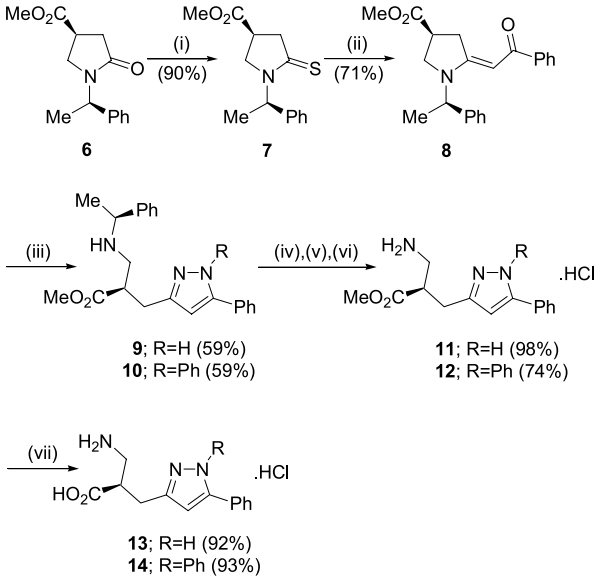


Scheme 1.



Scheme 2. Reagents and conditions: (i) Lawesson's reagent, THF, rt, 3–4 h; (ii) $PhCOCH_2Br$, Ph_3P, Et_3N, $MeCN–CH_2Cl_2$, rt, 24 h; (iii) $RNHNH_2 \cdot HCl$, MeOH or EtOH, reflux, 18–32 h, $NH_3–CHCl_3$; (iv) HCOOH or cyclohexene, 10% Pd–C, reflux, 6–18 h; (v) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C, 2–3 h; (vi) MeOH–HCl, 0→25 °C, 12 h; (vii) 6 N HCl, reflux 2–4 h.

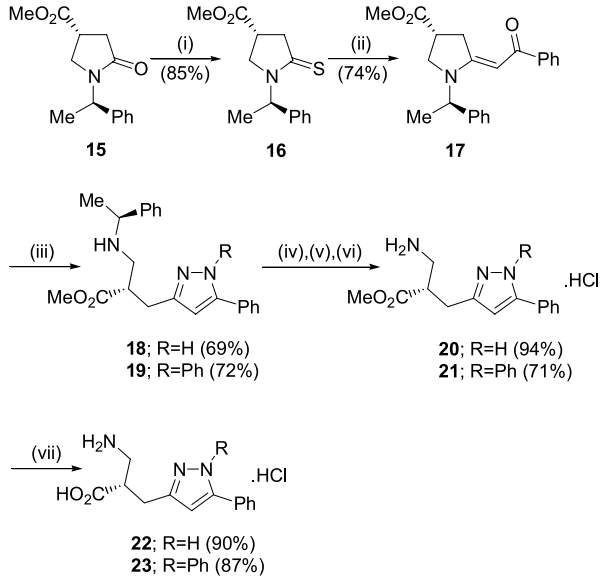
3-carboxylic acid methyl esters (**3**) in good yields. These enaminones **3** on condensation with hydroxyl amine/(un)substituted hydrazines hydrochloride in EtOH under reflux temperature underwent facile ring-chain-transformation reaction[8] to give 2-methylamino-methyl-3-[1-(un)substituted-5-aryl-1*H*-pyrazol-3-yl/5-aryl-isoxazol-3-yl]-propionic acid methyl ester hydrochloride (**4** and **5**) in 62–82% yields (Scheme 1).

Attempted reaction of these enaminones with 1,3-dinucleophiles such as guanidine, benzamidine, acetamidine, urea, and thiourea were unsuccessful. Compounds of type **3**, **4** and **5** are hitherto unknown in the literature and their structures were confirmed on the basis of elemental and spectroscopic analysis.

Having established the route to racemic ω-heterocyclic-β-amino acid esters, attention was turned to the synthesis of optically pure ω-heterocyclic-β-amino acids. (*R*)-(+)-1-Phenyl-ethylamine was used as chiral auxiliary to function both as resolving agent and protecting group during synthesis. The required (1*R*,3*R*)-5-oxo-1-(1-phenyl-ethyl)-pyrrolidine-3-carboxylic acid methyl ester **6** and (1*R*,3*S*)-5-oxo-1-(1-phenyl-ethyl)-pyrrolidine-3-carboxylic acid methyl ester **15** were prepared from itaconic acid and (*R*)-(+)-1-phenyl-ethylamine as described in literature.[9] The purity and stereochemical homogeneity of **6** and **15** were established by TLC analysis, ^{1}H NMR and HPLC analysis and each isomer was found to be free from any contamination from other isomer. The optically pure methyl ester **6** was converted to corresponding thiolactam **7** in 90% yields following the procedure described in literature.[6] Sulfur extrusion reaction on thiolactam **7** with phenacyl bromide yielded the enaminone **8** in 71% yield (Scheme 2). The enaminone **8** was next subjected to ring-chain-transformation with hydrazine hydrochloride and phenyl-hydrazine hydrochloride to afford (1*R*,2*R*)-2-[(1-phenyl-ethylamino)-methyl]-3-(5-phenyl-1*H*-pyrazol-3-yl)-propionic acid methyl ester **9** and (1*R*,2*R*)-3-(1,5-diphenyl-1*H*-pyrazol-3-yl)-2-[(1-phenyl-ethylamino)-methyl]-propionic acid methyl ester **10**, respectively, in 59% yields (Scheme 2). The *N*-debenzylation of compounds **9** and **10** using catalytic transfer hydrogenation conditions[6] gave crude (2*R*)-2-aminomethyl-3-(5-phenyl-1*H*-pyrazol-3-yl)-propionic acid methyl ester **11** and (2*R*)-2-aminomethyl-3-(1,5-diphenyl-1*H*-pyrazol-3-yl)-propionic acid methyl ester **12**, respectively. These crude amino acid ester **11** and **12** were converted to corresponding *N*-Boc derivatives and then purified by column chromatography over silica gel to afford pure *N*-Boc analog, which on treatment with methanolic-HCl at low temperature to afford pure amino acid ester **11** and **12**, which were isolated as hydrochloride salts. Finally the acidic hydrolysis of the methyl esters **11** and **12** afforded the desired (2*R*)-2-aminomethyl-3-(5-phenyl-1*H*-pyrazol-3-yl)-propionic acid **13** and (2*R*)-2-aminomethyl-3-(1,5-diphenyl-1*H*-pyrazol-3-yl)-propionic acid **14**, respectively, in quantitative yields, which were isolated as hydrochloride salts (Scheme 2).

Following a similar sequence of reactions, (1*R*,3*S*)-5-oxo-1-(1-phenyl-ethyl)-pyrrolidine-3-carboxylic acid methyl ester **15** was converted to (2*S*)-2-aminomethyl-3-(5-phenyl-1*H*-pyrazol-3-yl)-propionic acid **22** and (2*S*)-2-aminomethyl-3-(1,5-diphenyl-1*H*-pyrazol-3-yl)-propionic acid **23** (Scheme 3).

All new compounds reported here, were fully characterized on the basis of complementary spectroscopic (IR, NMR and MS) and analytical data. Specific optical rotations of the antipodes were found to be opposite and identical.



Scheme 3. Reagents and conditions: (i) Lawesson's reagent, THF, rt, 3–4 h; (ii) $PhCOCH_2Br$, Ph_3P, Et_3N, MeCN–CH_2Cl_2, rt, 24 h; (iii) $RNHNH_2 \cdot HCl$, MeOH or EtOH, reflux, 18–32 h, NH_3–$CHCl_3$; (iv) HCOOH or cyclohexene, 10% Pd–C, reflux, 6–18 h; (v) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C, 2–3 h; (vi) MeOH–HCl, 0→25 °C, 12 h; (vii) 6 N HCl, reflux 2–4 h.

3. Conclusion

In conclusion, we have developed a convenient and new approach for the synthesis of ω-heterocyclic-β-amino acids from activated lactams derived from itaconic acid. This methodology can be used to afford the higher analogs, simply by extending either the lactam ring size or changing the position of carboxyl group on a given lactam. Further, investigation on this type of reaction is currently in progress in our laboratories.

4. Experimental

4.1. General

Melting points were recorded on a Büchi B-540 melting point apparatus. Compounds were routinely checked for their purity on silica gel 60 F_{254} 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 $KMnO_4$ reagents. IR spectra (λ_{max} in cm^{-1}) were recorded on Perkin Elmer Paragon-1000 PC instrument and NMR (300 MHz) spectra were recorded on Bruker 300-DRX instrument as solutions using TMS as internal standard, and chemical shifts are expressed in δ units. Mass spectra were recorded on PE-SCIEX LC-MS/MS instrument. Optical rotations were taken on Autopol-III instrument. Elemental analyses were carried out with a Perkin Elmer 2400 analyzer and values found were within $\pm 0.4\%$ of theoretical values.

4.2. 1-Methyl-5-thioxo-pyrrolidine-3-carboxylic acid methyl ester (2)

To a soln of lactam **1**[7] (15.07 g, 96 mmol) in dry THF (75 mL) was added Lawesson's reagent (19.4 g, 48 mmol) portion-wise under stirring at 25–30 °C and resulting reaction mixture stirred for 2–3 h at same temperature. THF was removed under reduced pressure to obtain a viscous residue, which was dissolved in EtOAc (200 mL), washed with 10% $NaHCO_3$ (5×50 mL), brine (50 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give the thiolactam **2** as viscous oil, yield 16.2 g (98%); ν_{max} (CH_2Cl_2) 1736, 1210 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.26 (s, 3H, NC*H*$_3$), 3.31–3.35 (m, 3H, 3-C*H*$_2$, 4-C*H*), 3.74 (s, 3H, CO_2CH_3), 3.90–3.97 (m, 1H, 5-C*H*$_a$), 4.04–4.09 (m, 1H, 5-C*H*$_b$); *m*/*z* 174 (M+1).

4.3. Sulfur extrusion reaction on thiolactam with phenacyl bromides

General procedure. To a soln of thiolactam **2** (5.0 mmol) in dry MeCN (2 mL), phenacyl bromide (6.25 mmol, 1.25 equiv) was added and the reaction mixture stirred for 10 h at 25–30 °C. The solid, which separated out, was dissolved by addition of dry CH_2Cl_2 (25 mL) and stirred for 10 min at the same temperature. To this Ph_3P (7.5 mmol) and Et_3N (15.0 mmol) were added and the reaction mixture stirred for another 14 h at same temperature. When the reaction was completed, solvents were removed under reduced pressure and the residue was dissolved in EtOAc (50 mL), washed with H_2O (3×10 mL), brine (10 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by column chromatography over silica gel (230–400 mesh) using hexanes–EtOAc gradient as eluent to afford enaminones **3a**–**3e**.

4.3.1. 1-Methyl-5-(2-oxo-2-phenyl-ethylidene)-pyrrolidine-3-carboxylic acid methyl ester (3a). This was obtained as colorless thick oil by condensing phenacyl bromide with thiolactam **2**, 67% yield; ν_{max} (CH_2Cl_2) 1735, 1626, 1579, 1546, 1217 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.96 (s, 3H, NC*H*$_3$), 3.20–3.25 (m, 1H, 4-C*H*), 3.61–3.67 (m, 2H, 3-C*H*$_2$), 3.73 (s, 3H, CO_2CH_3), 3.76–3.83 (m, 2H, 5-C*H*$_2$), 5.70 (s, 1H, COC*H*), 7.37–7.43 (m, 3H, Ar*H*), 7.86–7.80 (m, 2H, Ar*H*); δ_C (75 MHz, $CDCl_3$) 187.0, 174.5, 169.0, 136.7, 134.3, 129.7, 129.0, 93.5, 58.1, 50.7, 46.9, 36.2, 35.1; *m*/*z* 260 (M+1). Anal. Calcd for $C_{15}H_{17}NO_3$ (259.30): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.22; H, 6.53; N, 5.29%.

4.3.2. 1-Methyl-5-[2-(4-methoxyphenyl)-2-oxo-ethylidene]-pyrrolidine-3-carboxylic acid methyl ester (3b). This was obtained in 83% yield as white needles by condensing 4-methoxyphenacyl bromide with thiolactam **2**, mp 96–97 °C; ν_{max} (KBr) 1745, 1618, 1219 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.96 (s, 3H, NC*H*$_3$), 3.20–3.30 (m, 1H, 4-C*H*), 3.59–3.67 (m, 2H, 3-C*H*$_2$), 3.72 (s, 3H, CO_2CH_3), 3.75–3.81 (m, 2H, 5-C*H*$_2$), 3.84 (s, 3H, OC*H*$_3$), 5.68 (s, 1H, COC*H*), 6.89 (d, *J*=9.0 Hz, 2H, Ar*H*), 7.88 (d, *J*=9.0 Hz, 2H, Ar*H*); *m*/*z* 290 (M+1). Anal. Calcd for $C_{16}H_{19}NO_4$ (289.33): C, 66.42; H, 6.62; N, 4.84. Found: C, 66.54; H, 6.47; N, 4.44%.

4.3.3. 1-Methyl-5-[2-(4-nitrophenyl)-2-oxo-ethylidene]-pyrrolidine-3-carboxylic acid methyl ester (3c). This was obtained in 75% yield as yellow solid by condensing 4-nitrophenacyl bromide with thiolactam **2**, mp 102–103 °C; ν_{max} (KBr) 1741, 1625, 1598, 1542, 1344 cm^{-1};

δ_H (300 MHz, $CDCl_3$) 3.01 (s, 3H, NCH_3), 3.03–3.33 (m, 1H, 4-C*H*), 3.69–3.75 (m, 6H, CO_2CH_3, 3-CH_2, 5-CH_a), 3.84–3.89 (m, 1H, 5-CH_b), 5.64 (s, 1H, COC*H*), 7.99 (d, J=9.0 Hz, 2H, Ar*H*), 8.23 (d, J=9.0 Hz, 2H, Ar*H*); *m*/*z* 305 (M+1). Anal. Calcd for $C_{15}H_{16}N_2O_5$ (304.30): C, 59.21; H, 5.30; N, 9.21. Found: C, 58.90; H, 5.64; N, 9.29%.

4.3.4. 1-Methyl-5-[2-(4-bromophenyl)-2-oxo-ethylidene]-pyrrolidine-3-carboxylic acid methyl ester (3d). This was obtained in 53% yield as off white solid by condensing 4-bromophenacyl bromide with thiolactam **2**, mp 126–128 °C; ν_{max} (KBr) 1736, 1624, 1584, 1214, 976, 767 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.97 (s, 3H, NCH_3), 3.27–3.30 (m, 1H, 4-C*H*), 3.62–3.71 (m, 6H, CO_2CH_3, 3-CH_2, 5-CH_a), 3.78–3.84 (m, 1H, 5-CH_b), 5.62 (s, 1H, COC*H*), 7.51 (d, J=9.0 Hz, 2H, Ar*H*), 7.74 (d, J=9.0 Hz, 2H, Ar*H*); *m*/*z* 339 (M+1). Anal. Calcd for $C_{15}H_{16}BrNO_3$ (338.20): C, 53.27; H, 4.77; N, 4.14. Found: C, 53.11; H, 4.83; N, 3.92%.

4.3.5. 1-Methyl-5-[2-(4-chlorophenyl)-2-oxo-ethylidene]-pyrrolidine-3-carboxylic acid methyl ester (3e). This was obtained in 58% yield as thick oil by condensing 4-chlorophenacyl bromide with thiolactam **2**; ν_{max} ($CHCl_3$) 1735, 1573, 1542, 1216, 768 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.97 (s, 3H, NCH_3), 3.25–3.30 (m, 1H, 4-C*H*), 3.62–3.68 (m, 2H, 3-CH_2), 3.71 (s, 3H, CO_2CH_3), 3.73–3.84 (m, 2H, 5-CH_2), 5.63 (s, 1H, COC*H*), 7.35 (d, J=9.0 Hz, 2H, Ar*H*), 7.81 (d, J=9.0 Hz, 2H, Ar*H*); *m*/*z* 294 (M+1). Anal. Calcd for $C_{15}H_{16}ClNO_3$ (293.75): C, 61.33; H, 4.49; N, 4.77. Found: C, 61.49; H, 4.21; N, 4.70%.

4.4. Ring-chain-transformation reaction of enaminones with NH_2XH

General procedure. $NH_2XH\cdot HCl$ (2.99 mmol, 1.0 equiv) was added to a soln of enaminone **3** (2.99 mmol) in MeOH (10 mL) at 25–30 °C with stirring and the resulting reaction mixture was refluxed for 28 h. Solvent was removed under reduced pressure; the solid so obtained was stirred with Et_2O (20 mL) and filtered, dried under reduced pressure to afford **4a**–**4d** and **5**.

4.4.1. 2-Methylaminomethyl-3-[5-(4-nitrophenyl)-1*H*-pyrazol-3-yl]-propionic acid methyl ester hydrochloride (4a). This was obtained in 82% yield as white solid by condensing hydrazine dihydrochloride with enaminone **3c**, mp 190–191 °C; ν_{max} (KBr) 1739, 1601, 1524, 1342 cm^{-1}; δ_H (300 MHz, CD_3OD) 2.76 (s, 3H, NCH_3), 3.04–3.16 (m, 4H, 2×CH_2), 3.32–3.33 (m, 1H, 4-C*H*), 3.71 (s, 3H, CO_2CH_3), 6.68 (s, 1H, Ar*H*), 7.90 (d, J=9.0 Hz, 2H, Ar*H*), 8.22 (d, J=9.0 Hz, 2H, Ar*H*); *m*/*z* 319 (M+1). Anal. Calcd for $C_{15}H_{18}N_4O_4\cdot 2HCl$ (391.25): C, 46.05; H, 5.15; N, 14.32. Found: C, 46.19; H, 4.96; N, 13.97%.

4.4.2. 3-[5-(4-Methoxyphenyl)-1*H*-pyrazol-3-yl]-2-methylaminomethyl-propionic acid methyl ester hydrochloride (4b). This was obtained as white powder by condensing hydrazine dihydrochloride with enaminone **3b**, which was recrystallized from MeOH–Et_2O to give colorless long needles (62% yield), mp 200–201 °C; ν_{max} (KBr) 1734, 1617 cm^{-1}; δ_H (300 MHz, TFA-*d*) 3.05 (s, 3H, NCH_3), 3.36–3.66 (m, 4H, 2×CH_2), 3.85 (br s, 1H, 4-C*H*), 3.91 (s, 3H, CO_2CH_3), 4.04 (s, 3H, OCH_3), 6.99 (s, 1H, Ar*H*), 7.21 (d, J=9.0 Hz, 2H, Ar*H*), 7.80 (d, J=9.0 Hz, 2H, Ar*H*); *m*/*z* 304 (M+1). Anal. Calcd for $C_{16}H_{21}N_3O_3\cdot 2HCl$ (376.28): C, 51.07; H, 6.16; N, 11.17. Found: C, 50.85; H, 6.13; N, 10.95%.

4.4.3. 3-[5-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl]-2-methylaminomethyl-propionic acid methyl ester hydrochloride (4c). This was obtained as off white solid by condensing phenyl hydrazine dihydrochloride with enaminone **3b**, which was recrystallized from MeOH–Et_2O to give off white solid (78% yield), mp 180–181 °C; ν_{max} (KBr) 1733, 1611, 1506, 1250 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.72 (s, 3H, NCH_3), 3.15–3.45 (m, 4H, 2×CH_2), 3.61–3.64 (m, 1H, 4-C*H*), 3.80 (s, 3H, CO_2CH_3), 3.82 (s, 3H, OCH_3), 6.32 (s, 1H, Ar*H*), 6.81 (d, J=9.0 Hz, 2H, Ar*H*), 7.12 (d, J=9.0 Hz, 2H, Ar*H*), 7.24–7.37 (m, 5H, Ar*H*); *m*/*z* 380 (M+1). Anal. Calcd for $C_{22}H_{25}N_3O_3\cdot HCl$ (415.91): C, 63.53; H, 6.30; N, 10.10. Found: C, 63.39; H, 6.33; N, 10.08%.

4.4.4. 3-[1-(4-Fluorophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]-2-methylaminomethyl-propionic acid methyl ester hydrochloride (4d). This was obtained as off white solid by condensing 4-fluorophenyl hydrazine dihydrochloride with enaminone **3b**, which was recrystallized from MeOH–Et_2O to give white solid (81% yield), mp 162–163 °C; ν_{max} (KBr) 2944, 1733, 1613, 1512 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.69 (s, 3H, NCH_3), 2.93–3.37 (m, 4H, 2×CH_2), 3.55 (br s, 1H, 4-C*H*), 3.80 (br s, 6H, CO_2CH_3, OCH_3), 6.30 (s, 1H, Ar*H*), 6.81 (d, J=9.0 Hz, 2H, Ar*H*), 7.03 (d, J=9.0 Hz, 2H, Ar*H*), 7.06 (d, J=12.0 Hz, 2H, Ar*H*), 7.15 (d, J=9.0 Hz, 2H, Ar*H*); *m*/*z* 398 (M+1). Anal. Calcd for $C_{22}H_{24}FN_3O_3\cdot HCl$ (433.90): C, 60.90; H, 5.81; N, 9.68. Found: C, 61.13; H, 5.67; N, 9.80%.

4.4.5. 3-[5-(4-Methoxyphenyl)-isoxazol-3-yl]-2-methyl-aminomethyl-propionic acid methyl ester hydrochloride (5). This was obtained as gummy solid by condensing hydroxylamine hydrochloride with enaminone **3b**, which was recrystallized from MeOH–Et_2O to give white crystalline solid (74% yield), mp 139–140 °C; ν_{max} (KBr) 1731, 1618, 1444, 1255 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.79 (s, 3H, NCH_3), 3.25–3.49 (m, 4H, 2×CH_2), 3.70 (br s, 1H, 4-C*H*), 3.84 (s, 3H, CO_2CH_3), 3.87 (s, 3H, OCH_3), 6.45 (s, 1H, Ar*H*), 6.97 (d, J=9.0 Hz, 2H, Ar*H*), 7.70 (d, J=9.0 Hz, 2H, Ar*H*); *m*/*z* 305 (M+1). Anal. Calcd for $C_{16}H_{20}N_2O_4\cdot HCl$ (340.80): C, 56.39; H, 6.21; N, 8.22. Found: C, 56.34; H, 6.37; N, 8.15%.

4.5. (1*R*,3*R*)-5-Oxo-1-(1-phenyl-ethyl)-pyrrolidine-3-carboxylic acid methyl ester (6) and (1*R*,3*S*)-5-oxo-1-(1-phenyl-ethyl)-pyrrolidine-3-carboxylic acid methyl ester (15)

The compounds **6** and **15** were prepared according to the literature method.[9]

Compound **6** was isolated as oil in 41% yield; ν_{max} (CH_2Cl_2) 1732, 1680, 1492, 1430 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.53 (d, J=7.0 Hz, 3H, CHCH_3), 2.63–2.80 (m, 2H, 3-CH_2), 3.07–3.22 (m, 2H, 5-CH_2), 3.51–3.62 (m, 1H, 4-C*H*), 3.72 (s, 3H, CO_2CH_3), 5.50 (q, J=7.0 Hz, 1H, C*H*CH_3),

7.26–7.31 (m, 5H, Ar*H*); *m/z* 248 (M+1); $[\alpha]_D^{24}$ +52.9 (*c* 1, MeOH) {lit.,[9] $[\alpha]_D^{24}$ +51.3 (*c* 2.1, EtOAc)}. Anal. Calcd for $C_{14}H_{17}NO_3$ (247.29): C, 68.00; H, 6.93; N, 5.66. Found: C, 67.81; H, 6.66; N, 5.95%.

Compound **15** was isolated in 47% yield as long needles, mp 68–69 °C (lit.,[9] mp 70 °C); ν_{max} (KBr) 1736, 1682, 1493, 1434 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.56 (d, *J*=7.0 Hz, 3H, CHC*H*$_3$), 2.69–2.79 (m, 2H, 3-C*H*$_2$), 3.16–3.25 (m, 2H, 5-C*H*$_2$), 3.52–3.60 (m, 1H, 4-C*H*), 3.67 (s, 3H, CO_2CH_3), 5.52 (q, *J*=7.0 Hz, 1H, C*H*CH$_3$), 7.30–7.40 (m, 5H, Ar*H*); *m/z* 248 (M+1); $[\alpha]_D^{24}$ +107.2 (*c* 1, MeOH) {lit.,[9] $[\alpha]_D^{24}$ +109.6 (*c* 2.6, EtOAc)}. Anal. Calcd for $C_{14}H_{17}NO_3$ (247.29): C, 68.00; H, 6.93; N, 5.66. Found: C, 68.05; H, 7.13; N, 5.49%.

4.6. (1*R*,3*R*)-1-(1-Phenyl-ethyl)-5-thioxo-pyrrolidine-3-carboxylic acid methyl ester (7)

This was obtained from **6** as thick oil in 90% yield according to the procedure described for compound **2**; ν_{max} (CH_2Cl_2) 1737, 1495, 1443 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.61 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$), 3.13 (dd, *J*=7.2, 8.7 Hz, 1H, 3-C*H*$_a$), 3.31–3.43 (m, 3H, 3-C*H*$_b$ and 5-C*H*$_2$), 3.72 (s, 3H, CO_2CH_3), 3.86 (dd, *J*=6.3, 6.1 Hz, 1H, 4-C*H*), 6.34 (q, *J*=7.2 Hz, 1H, C*H*CH$_3$), 7.31–7.35 (m, 5H, Ar*H*); *m/z* 264 (M+1); $[\alpha]_D^{24}$ +70.9 (*c* 1, MeOH). Anal. Calcd for $C_{14}H_{17}NO_2S$ (263.36): C, 63.85; H, 6.51; N, 5.32. Found: C, 63.78; H, 6.42; N, 5.28%.

4.7. (1*R*,3*S*)-1-(1-Phenyl-ethyl)-5-thioxo-pyrrolidine-3-carboxylic acid methyl ester (16)

This was obtained from **15** as thick oil in 85% yield according to the procedure described for compound **2**; ν_{max} (CH_2Cl_2) 1737, 1495, 1451 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.61 (d, *J*=7.2 Hz, 3H, CHC*H*$_3$), 3.20–3.60 (m, 4H, 3-C*H*$_2$ and 5-C*H*$_2$), 3.64 (s, 3H, CO_2CH_3), 3.74–3.81 (m, 1H, 4-C*H*), 6.36 (q, *J*=7.2 Hz, 1H, C*H*CH$_3$), 7.30–7.40 (m, 5H, Ar*H*); *m/z* 264 (M+1); $[\alpha]_D^{24}$ +133 (*c* 1, MeOH). Anal. Calcd for $C_{14}H_{17}NO_2S$ (263.36): C, 63.85; H, 6.51; N, 5.32. Found: C, 63.90; H, 6.67; N, 5.21%.

4.8. (1*R*,3*R*)-5-(2-Oxo-2-phenyl-ethylidene)-1-(1-phenyl-ethyl)-pyrrolidine-3-carboxylic acid methyl ester (8)

This was obtained in 71% yield as light yellow solid by condensing phenacyl bromide with thiolactam **7** according to the procedure described for compound **3**, mp 89–90 °C; ν_{max} (KBr) 1733, 1625, 1532, 1374 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.66 (d, *J*=6.9 Hz, 3H, CHC*H*$_3$), 3.13–3.37 (m, 2H, 3-C*H*$_2$), 3.61–3.69 (m, 2H, 5-C*H*$_2$), 3.72 (s, 3H, CO_2CH_3), 3.87 (dd, *J*=9.3, 9.6 Hz, 1H, 4-C*H*), 5.09 (q, *J*=6.9 Hz, 1H, C*H*CH$_3$), 5.93 (s, 1H, COC*H*), 7.28–7.44 (m, 8H, Ar*H*), 7.80–7.83 (m, 2H, Ar*H*); δ_C (75 MHz, $CDCl_3$) 187.0, 174.5, 169.0, 137.2, 136.7, 134.3, 129.7, 129.0, 128.3, 128.1, 126.8, 93.5, 53.7, 53.0, 50.7, 47.5, 35.7, 22.3; *m/z* 350 (M+1); $[\alpha]_D^{24}$ +341.1 (*c* 0.7, MeOH). Anal. Calcd for $C_{22}H_{23}NO_3$ (349.42): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.63; H, 6.77; N, 4.15%.

4.9. (1*R*,3*S*)-5-(2-Oxo-2-phenyl-ethylidene)-1-(1-phenyl-ethyl)-pyrrolidine-3-carboxylic acid methyl ester (17)

This was obtained in 74% yield as light yellow thick oil by condensing phenacyl bromide with thiolactam **16** according to the procedure described for compound **3**; ν_{max} (CH_2Cl_2) 1735, 1625, 1576, 1539 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.65 (d, *J*=6.9 Hz, 3H, CHC*H*$_3$), 3.20–3.25 (m, 2H, 3-C*H*$_2$), 3.54–3.64 (m, 5H, 5-C*H*$_2$, CO_2CH_3), 3.75–3.78 (m, 1H, 4-C*H*), 5.05 (q, *J*=7.0 Hz, 1H, C*H*CH$_3$), 5.86 (s, 1H, COC*H*), 7.29–7.41 (m, 8H, Ar*H*), 7.67–7.79 (m, 2H, Ar*H*); *m/z* 350 (M+1); $[\alpha]_D^{24}$ +168.6 (*c* 0.7, MeOH). Anal. Calcd for $C_{22}H_{23}NO_3$ (349.42): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.81; H, 6.59; N, 3.95%.

4.10. (1*R*,2*R*)-2-[(1-Phenyl-ethylamino)-methyl]-3-(5-phenyl-1*H*-pyrazol-3-yl)-propionic acid methyl ester (9)

This was obtained in 59% yield as oil by condensing hydrazine dihydrochloride with enaminone **8** according to the procedure described for compound **4**; ν_{max} (CH_2Cl_2) 3208, 2905, 1732, 1568, 1436 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.35 (d, *J*=6.8 Hz, 3H, CHC*H*$_3$), 2.69–2.79 (m, 2H, NC*H*$_2$), 2.86–2.94 (m, 2H, CHC*H*$_2$), 2.99–3.05 (m, 1H, C*H*CO$_2$CH$_3$), 3.68 (s, 3H, CO_2CH_3), 3.75 (q, *J*=6.0 Hz, 1H, C*H*CH$_3$), 6.28 (s, 1H, Ar*H*), 7.21–7.41 (m, 8H, Ar*H*), 7.67–7.70 (m, 2H, Ar*H*); *m/z* 364 (M+1); $[\alpha]_D^{24}$ +19.2 (*c* 0.5, MeOH). Anal. Calcd for $C_{22}H_{25}N_3O_2$ (363.45): C, 72.70; H, 6.93; N, 11.56. Found: C, 72.99; H, 6.90; N, 11.39%.

4.11. (1*R*,2*S*)-2-[(1-Phenyl-ethylamino)-methyl]-3-(5-phenyl-1*H*-pyrazol-3-yl)-propionic acid methyl ester (18)

This was obtained in 69% yield as thick oil by condensing hydrazine dihydrochloride with enaminone **17** according to the procedure described for compound **4**; ν_{max} (CH_2Cl_2) 3344, 2923, 1732, 1493, 1463 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.30 (d, *J*=6.8 Hz, 3H, CHC*H*$_3$), 2.60–2.85 (m, 2H, NC*H*$_2$), 2.90–3.06 (m, 3H, CHC*H*$_2$, C*H*CO$_2$CH$_3$), 3.65 (s, 3H, CO_2CH_3), 3.78 (q, *J*=7.0 Hz, 1H, C*H*CH$_3$), 6.30 (s, 1H, Ar*H*), 7.22–7.41 (m, 8H, Ar*H*), 7.68–7.70 (m, 2H, Ar*H*); *m/z* 364 (M+1); $[\alpha]_D^{24}$ +15.9 (*c* 0.51, MeOH). Anal. Calcd for $C_{22}H_{25}N_3O_2$ (363.45): C, 72.70; H, 6.93; N, 11.56. Found: C, 72.57; H, 7.03; N, 11.60%.

4.12. (1*R*,2*R*)-3-(1,5-Diphenyl-1*H*-pyrazol-3-yl)-2-[(1-phenyl-ethylamino)-methyl]-propionic acid methyl ester (10)

This was obtained in 59% yield as thick oil by condensing phenylhydrazine with enaminone **8** according to the procedure described for compound **4**; ν_{max} (CH_2Cl_2) 1739, 1696, 1610, 1585 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.28 (d, *J*=6.6 Hz, 3H, CHC*H*$_3$), 2.70–2.74 (m, 2H, NC*H*$_2$), 2.79–2.88 (m, 1H, C*H*CO$_2$CH$_3$), 3.01–3.06 (m, 2H, CHC*H*$_2$), 3.67 (s, 3H, CO_2CH_3), 3.74 (q, *J*=6.8 Hz, 1H, C*H*CH$_3$), 6.16 (s, 1H, Ar*H*), 7.11–7.26 (m, 15H, Ar*H*); *m/z* 440 (M+1); $[\alpha]_D^{24}$ +20.0 (*c* 0.25, MeOH). Anal. Calcd for $C_{28}H_{29}N_3O_2$ (439.55): C, 76.51; H, 6.65; N, 9.56. Found: C, 76.29; H, 6.49; N, 9.77%.

4.13. (1*R*,2*S*)-3-(1,5-Diphenyl-1*H*-pyrazol-3-yl)-2-[(1-phenyl-ethylamino)-methyl]-propionic acid methyl ester (19)

This was obtained in 72% yield as thick oil by condensing phenylhydrazine with enaminone **17** according to the procedure described for compound **4**; ν_{max} (CH_2Cl_2) 1743, 1695, 1619, 1595 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.31 (d, J= 6.6 Hz, 3H, CHCH_3), 2.04 (br s, 1H, N*H*), 2.67 (dd, J=7.2, 5.7 Hz, 2H, NCH_2), 2.83–3.07 (m, 3H, CHCH_2, C*H*CO_2-CH_3), 3.70 (s, 3H, CO_2CH_3), 3.73 (q, J=6.9 Hz, 1H, C*H*CH_3), 6.23 (s, 1H, Ar*H*), 7.15–7.36 (m, 15H, Ar*H*); *m*/*z* 440 (M+1); $[\alpha]_D^{24}$ +29.0 (*c* 0.41, MeOH). Anal. Calcd for $C_{28}H_{29}N_3O_2$ (439.55): C, 76.51; H, 6.65; N, 9.56. Found: C, 76.31; H, 6.58; N, 9.60%.

4.14. General method of *N*-debenzylation

Method 1. A mixture of *N*-(phenyl-ethyl)-amino acid esters (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 rt and filtered through Celite bed, washed with EtOH (2×5 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 it with ethereal-HCl or else its *N*-Boc derivative was prepared.

Purification of amino acid esters. General method for N-Boc protection. To a stirred solution of crude amino acid ester (1 equiv) in CH_2Cl_2 (20 mL) was added Boc anhydride (1.1 equiv) and Et_3N (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 reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with chilled 10% $NaHCO_3$ (3×50 mL), brine (50 mL), dried (Na_2SO_4) 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 0.5% MeOH–$CHCl_3$ as eluent to afford pure *N*-Boc derivative of amino acid ester.

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

Method 2. A mixture of *N*-(phenyl-ethyl)-amino acid esters (1.0 g), 10% Pd–C (0.5 g), cyclohexene (150 mL) was refluxed with stirring for 6–18 h. After completion of reaction, reaction mixture was cooled to rt and filtered through a Celite bed, washed with EtOH (2×5 mL) and the combined filtrate was concentrated under reduced pressure to afford crude amino acid esters, which was purified as described above in Method 1.

Using the above described methods were prepared:

4.14.1. (2*R*)-2-Aminomethyl-3-(5-phenyl-1*H*-pyrazol-3-yl)-propionic acid methyl ester hydrochloride (11).

Method 1. This was isolated in 98% yield as white hydrochloride salt from compound **9**, mp 183–184 °C; ν_{max} (KBr) 3420, 1750, 1623, 1593 cm^{-1}; δ_H (300 MHz, D_2O) 3.17–3.67 (m, 5H, NCH_2, C*H*CH_2), 3.75 (s, 3H, CO_2CH_3), 6.77 (s, 1H, Ar*H*), 7.48–7.60 (m, 3H, Ar*H*), 7.68–7.75 (m, 2H, Ar*H*); *m*/*z* 260 (M+1); $[\alpha]_D^{24}$ +18.3 (*c* 0.7, MeOH). Anal. Calcd for $C_{14}H_{17}N_3O_2 \cdot 2HCl$ (332.23): C, 50.61; H, 5.76; N, 12.65. Found: C, 50.63; H, 5.88; N, 12.96%.

4.14.2. (2*R*)-2-Aminomethyl-3-(1,5-diphenyl-1*H*-pyrazol-3-yl)-propionic acid methyl ester hydrochloride (12).

Method 2. This was isolated in 74% yield as off white hydrochloride salt from compound **10**, mp 59–60 °C; ν_{max} (KBr) 3473, 2944, 1740, 1618, 1603, 1492 cm^{-1}; δ_H (300 MHz, D_2O) 2.98–3.00 (d, J=4.7 Hz, 2H, NCH_2), 3.12–3.28 (m, 3H, C*H*CH_2), 3.63 (s, 3H, CO_2CH_3), 6.38 (s, 1H, Ar*H*), 7.09–7.53 (m, 10H, Ar*H*); *m*/*z* 336 (M+1); $[\alpha]_D^{24}$ +5.6 (*c* 0.7, MeOH). Anal. Calcd for $C_{20}H_{21}N_3O_2 \cdot 2HCl$ (408.32): C, 58.83; H, 5.68; N, 10.29. Found: C, 59.01; H, 5.80; N, 10.26%.

4.14.3. (2*S*)-2-Aminomethyl-3-(5-phenyl-1*H*-pyrazol-3-yl)-propionic acid methyl ester hydrochloride (20).

Method 1. This was isolated in 94% yield as off white hydrochloride salt from compound **18**, mp 199–200 °C; ν_{max} (KBr) 3427, 1738, 1623, 1595, 1585 cm^{-1}; δ_H (300 MHz, D_2O) 3.17–3.65 (m, 5H, NCH_2, C*H*CH_2), 3.77 (s, 3H, CO_2CH_3), 6.77 (s, 1H, Ar*H*), 7.53–7.55 (m, 3H, Ar*H*), 7.69–7.75 (m, 2H, Ar*H*); *m*/*z* 260 (M+1); $[\alpha]_D^{24}$ −18.0 (*c* 0.66, MeOH). Anal. Calcd for $C_{14}H_{17}N_3O_2 \cdot 2HCl$ (332.23): C, 50.61; H, 5.76; N, 12.65. Found: C, 50.59; H, 5.77; N, 12.51%.

4.14.4. (2*S*)-2-Aminomethyl-3-(1,5-diphenyl-1*H*-pyrazol-3-yl)-propionic acid methyl ester hydrochloride (21).

Method 2. This was isolated in 71% yield as white hydrochloride salt from compound **19**, mp 62–63 °C; ν_{max} (KBr) 3469, 2939, 1753, 1620, 1595, 1499 cm^{-1}; δ_H (300 MHz, D_2O) 3.22 (d, J=4.8 Hz, 2H, NCH_2), 3.33–3.48 (m, 3H, C*H*CH_2), 3.84 (s, 3H, CO_2CH_3), 6.62 (s, 1H, Ar*H*), 7.36–7.52 (m, 10H, Ar*H*); *m*/*z* 336 (M+1); $[\alpha]_D^{24}$ −5.7 (*c* 0.79, MeOH). Anal. Calcd for $C_{20}H_{21}N_3O_2 \cdot 2HCl$ (408.32): C, 58.83; H, 5.68; N, 10.29. Found: C, 58.79; H, 5.58; N, 10.20%.

4.15. General method for ester hydrolysis

A soln of amino acid ester hydrochloride (1.0 g) in 6 N HCl soln (5 mL) was refluxed under stirring for 4–6 h after cooled to rt this was washed with Et_2O (3×15 mL). The aq layer was concentrated under reduced pressure to afford corresponding amino acid hydrochloride. Using the above described methods were prepared:

4.15.1. (2*R*)-2-Aminomethyl-3-(5-phenyl-1*H*-pyrazol-3-yl)-propionic acid hydrochloride (13).

This was isolated in 92% yield as off white hydrochloride salt from compound **11**, mp 133–134 °C; ν_{max} (KBr) 3420, 1725, 1620, 1489 cm^{-1}; δ_H (300 MHz, D_2O) 3.17–3.35 (m, 5H, NCH_2, C*H*CH_2), 6.78 (s, 1H, Ar*H*), 7.53–7.55 (m, 3H,

Ar*H*), 7.71–7.72 (m, 2H, Ar*H*); δ_C (75 MHz, D_2O) 179.5, 152.9, 145.5, 136.5, 129.0, 128.5, 127.0, 104.3, 50.6, 41.4, 26.7; *m*/*z* 246 (M+1); $[\alpha]_D^{24}$ +8.2 (*c* 0.72, H_2O). Anal. Calcd for $C_{13}H_{15}N_3O_2 \cdot 2HCl$ (318.20): C, 49.07; H, 5.38; N, 13.21. Found: C, 48.87; H, 5.15; N, 13.10%.

4.15.2. (2*R*)-2-Aminomethyl-3-(1,5-diphenyl-1*H*-pyrazol-3-yl)-propionic acid hydrochloride (14). This was isolated in 93% yield as off white hydrochloride salt from compound **12**, mp 166–167 °C; ν_{max} (KBr) 3434, 3055, 2943, 1717, 1597, 1503 cm^{-1}; δ_H (300 MHz, D_2O) 3.02 (br s, 2H, NCH_2), 3.20–3.28 (m, 3H, CHCH_2), 6.38 (s, 1H, Ar*H*), 6.65–7.00 (m, 7H, Ar*H*), 7.10–7.20 (m, 3H, Ar*H*); δ_C (75 MHz, D_2O) 179.5, 152.9, 145.8, 139.7, 136.5, 129.1, 129.0, 128.5, 127.0, 126.0, 118.8, 106.9, 50.6, 41.4, 27.0; *m*/*z* 322 (M+1); $[\alpha]_D^{24}$ +1.9 (*c* 1.05, H_2O). Anal. Calcd for $C_{19}H_{19}N_3O_2 \cdot 2HCl$ (394.29): C, 57.88; H, 5.37; N, 10.66. Found: C, 58.10; H, 5.31; N, 10.39%.

4.15.3. (2*S*)-2-Aminomethyl-3-(5-phenyl-1*H*-pyrazol-3-yl)-propionic acid hydrochloride (22). This was isolated in 90% yield as off white hydrochloride salt from compound **20**, mp 145–146 °C; ν_{max} (KBr) 3417, 1726, 1620, 1468 cm^{-1}; δ_H (300 MHz, D_2O) 3.18–3.35 (m, 5H, NCH_2, CHCH_2), 6.83 (s, 1H, Ar*H*), 7.50–7.60 (m, 3H, Ar*H*), 7.69–7.74 (m, 2H, Ar*H*); *m*/*z* 246 (M+1); $[\alpha]_D^{24}$ −8.1 (*c* 0.7, H_2O). Anal. Calcd for $C_{13}H_{15}N_3O_2 \cdot 2HCl$ (318.20): C, 49.07; H, 5.38; N, 13.21. Found: C, 49.08; H, 5.21; N, 13.33%.

4.15.4. (2*S*)-2-Aminomethyl-3-(1,5-diphenyl-1*H*-pyrazol-3-yl)-propionic acid hydrochloride (23). This was isolated in 87% yield as white hydrochloride salt from compound **21**, mp 194–195 °C; ν_{max} (KBr) 3448, 3047, 2939, 1717, 1597, 1503 cm^{-1}; δ_H (300 MHz, D_2O) 3.02 (br s, 2H, NCH_2), 3.11–3.28 (m, 3H, CHCH_2), 6.45 (s, 1H, Ar*H*), 7.10–7.36 (m, 10H, Ar*H*); *m*/*z* 322 (M+1); $[\alpha]_D^{24}$ −1.8 (*c* 1, H_2O). Anal. Calcd for $C_{19}H_{19}N_3O_2 \cdot 2HCl$ (394.29): C, 57.88; H, 5.37; N, 10.66. Found: C, 57.81; H, 5.33; N, 10.59%.

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