Synthesis of Optically Active α-Amino Acids Containing Pyrazolyl Ring as Substituent

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Abstract: Starting from commercially available L-serine, some pyrazolyl oxazolidines have been prepared and transformed into novel chiral α-amino acids, containing a pyrazole ring, which can be regarded as building blocks for peptidomimetics.

Key words: amino acids, cycloadditions, heterocycles, hydrazones, regioselectivity

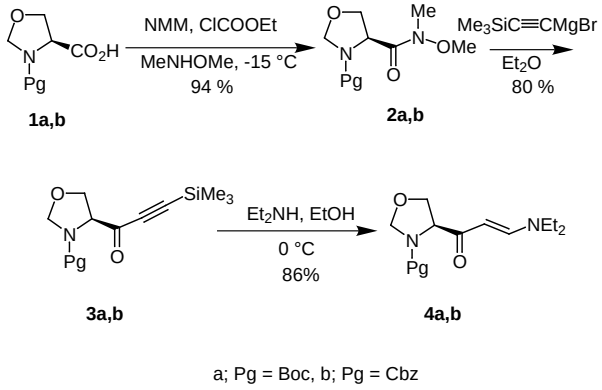
There is currently considerable interest in the synthesis of unusual and unnatural amino acids and their incorporation into peptides and proteins. Peptides composed of unnatural amino acids display often intriguing secondary structures and have shown potential as medicinal agents. In particular, they display improved metabolic stability for proteases compared to peptides composed of natural amino acids.

In the last few years we were interested in the preparation of unusual amino acids containing heterocyclic moieties.[2,3] These heterocyclic products are not only themselves of interest but are also valuable building blocks for peptidomimetics, in connection with the design and synthesis of drug candidates and as chiral starting materials for many applications. Thus, there is interest in the discovery and development of synthetic methodologies for the preparation of new enantiopure α-amino acids either through asymmetric synthesis[4] or modification of natural amino acids.[5]

We have previously reported a synthetic approach to a series of new chiral optically active α-amino acids containing 1,3- or 1,5-substituted pyrazolyl ring.[3] Continuing our interest in this area, we have sought to develop this method for generating and elaborating analogous functionalized heterocycles.

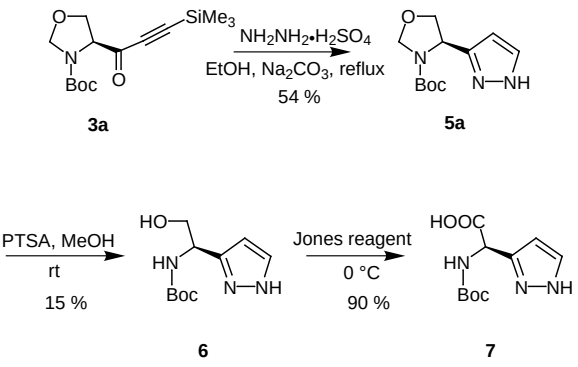
Similar to other cases, our strategy was based on the possibility of building the amino acid derivative from L-serine through the proper intermediate. Our previous work in this field indicated that the best method to prepare heterocyclic rings, such as pyrazoles and isoxazoles was the cyclocondensation of an α-alkynyl ketone with a nucleophile such as hydroxylamine or a hydrazine derivative. Moreover the reaction can be carried out in a regioselective manner by employing trimethylsilylethynyl ketones.[4,5]

Therefore, for the synthesis of the target compounds L-serine was converted into *N*-protected (*S*)-4-carboxyoxazolidine **1**,[6] from which compounds **3** and **4** were obtained via the Weinreb amide **2**, by a previously tested procedure,[3] in good yields (Scheme 1).



Scheme 1

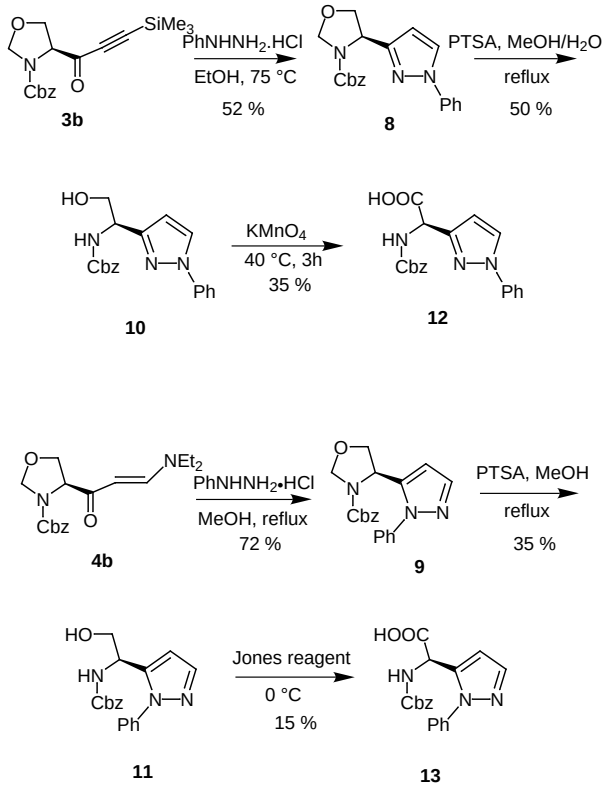
Surprisingly, compounds **3a** and **4a** (with Boc as *N*-protecting group) do not condense at all with hydroxylamine or phenylhydrazine,[7] and only the reaction with hydrazine gave the 4-[1*H*-pyrazol-3(5)-yl]oxazolidine-3-carboxylic acid *tert*-butyl ester (**5a**) in 54% yield (Scheme 2).



Scheme 2

The successive cleavage of the oxazolidine ring was performed without affecting the *N*-Boc protection using *p*-toluenesulfonic acid (PTSA) in anhydrous methanol at room temperature. Under these conditions, the reaction occurs with low conversion (15% after 24 h) affording the amino alcohol **6**. Subsequent oxidation under Jones' con-

ditions afforded (*R*)-*N*-*tert*-butoxycarbonylamino-(1*H*-pyrazol-3(5)-yl)-acetic acid (**7**) in 90% yield. In a similar manner, the *N*-Cbz derivatives **3b** and **4b** react with phenylhydrazine to give compounds **8** and **9**, respectively, in good yield. In these cases, the oxazolidine ring is remarkably resistant to cleavage and compound **8** was only cleaved using PTSA in methanol/water at 75 °C whereas transformation of **9** required anhydrous methanol at the same temperature (Scheme 3).



Scheme 3

Numerous methods are reported in the literature for the direct conversion of primary alcohols to the corresponding carboxylic acids, nevertheless this transformation is often a challenge. Although we have previously observed satisfactory results in the oxidation of analogous substrates with Jones' reagent, the amino alcohols **10** and **11** were found to be particularly inert towards common oxidizing agents. Sharpless reagent,[8] pyridinium chlorochromate (PCC) and other more recent methods[9] were ineffective and only use of $KMnO_4$ had succeeded in obtaining the pyrazolyl amino acid **12**, while only Jones' reagent oxidized compound **11** to **13**, at 0 °C with partial decomposition of the substrate.[10]

In conclusion, a methodology for the preparation of a new class of α-amino acids has been developed using an inexpensive chiral starting material. Further efforts on the possibility to carry out the synthesis of heterocyclic amino acids through solid phase procedures are currently in progress.

Bulb to bulb distillations were carried out with a Büchi GRK-51 apparatus equipped with a vacuum controller Büchi B-168. Elemental analyses were performed on a Perkin-Elmer 420 B analyzer. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) Fourier transform spectra were obtained with a Varian VXR-300 spectrometer in $CDCl_3$ using TMS as an intternal standard, unless otherwise specified. All reactions involving air sensitive materials were carried out under argon; all reagents and solvents employed were reagent grade materials purified by standard methods and distilled before use. Petroleum ether used had bp 35–60 °C. As chiral starting material L-serine of "*BioChemica*" grade (chemical and enantiomeric purity >95%) purchased from Fluka Chemie AG was used. (*S*)-*N*-Boc- (**1a**) and (*S*)-*N*-Cbz-4-carboxyoxazolidine (**1b**) were prepared according reported procedures.[6]

(*S*)-4-(*N*-Methoxy-*N*-methylcarbamoyl)oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (2a); Typical Procedure

Under vigorous stirring at −15 °C, 4-methylmorpholine (5.1 mL, 46.3 mmol) in CH_2Cl_2 (20 mL) and ethyl chloroformate (8.4 mL, 88.8 mmol) in CH_2Cl_2 (20 mL) were added to **1a** (10 g, 46.0 mmol) in CH_2Cl_2 (60 mL). The mixture was stirred at −15 °C for 15 min, then 4-methylmorpholine (10 mL, 90 mmol) and *N*,*O*-dimethylhydroxylamine (8.8 g, 90 mmol) were added portionwise. The resulting mixture was stirred at −15 °C for 1 h and at r.t. 12 h, and then treated with H_2O (100 mL). After separation of the organic layer, the aqueous phase was extracted with EtOAc (25 mL) and the combined organic layers were washed with 10% aq $NaHCO_3$, brine, 5% aq HCl and brine (25 mL each) in that order, and dried (Na_2SO_4).The solvent was evaporated under reduced pressure and the crude product, after purification by flash chromatography (SiO_2, EtOAc/hexane, 7:3) yielded **2a** as a colorless oil (11.2 g, 94%).

^{1}H NMR: δ = 1.45 (s, 9 H), 3.20 (br s, 3 H), 3.72 (br s, 3 H), 3.91 (m, 1 H), 4.27 (br, 1 H), 4.59−5.12 (m, 3 H).

^{13}C NMR: δ = 29.2, 33.5, 52.3, 64.9, 70.9, 74.0, 81.9, 156.0, 172.0.

Anal. calcd for $C_{11}H_{20}N_2O_5$: C, 50.76; H, 7.74; N, 10.76. Found C, 50.69; H, 7.74; N, 10.77.

(*S*)-4-(*N*-Methoxy-*N*-methylcarbamoyl)oxazolidine-3-carboxylic Acid Benzyl Ester (2b)

Compound **2b** was prepared accordingly, starting from **1b** (8.8 g, 35 mmol). The crude product obtained was purified by flash chromatography (SiO_2, EtOAc, hexane 6:4) to give pure **2b** as colorless oil (9.7 g, 94%).

^{1}H NMR (mixture of two conformers): δ = 3.15 (br s, 1.8 H,), 3.23 (br s, 1.2 H), 3.48 (br s, 1.2 H), 3.79 (br s 1.8 H), 3.96 (m, 1 H), 4.32 (m, 1 H), 4.69−4.89 (m, 1 H), 4.93−5.01 (m, 1 H), 5.12 (br s, 2 H), 5.15−5.24 (br m, 1 H), 7.34 (br s, 5 H).

^{13}C NMR: δ = 33.5, 52.9, 63.9, 72.9, 81.3, 127.2,127.5,128,8,141.0, 156.0, 171.8.

Anal. calcd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found C, 57.11; H, 6.14; N, 9.55.

(*S*)-4-[3-(Trimethylsilanyl)propynoyl]oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (3a); Typical Procedure

To a solution of ethylmagnesium bromide (50 mmol) in anhyd Et_2O (50 mL) was added a solution of trimethylsilylacetylene (4.9 g, 50 mmol) in Et_2O (20 mL) under stirring and then heated until formation of a white suspension. The mixture was cooled to 0 °C and compound **2a** (10.8 g, 36.6 mmol) in anhydrous Et_2O (25 mL) was added over a period of 5 min. The mixture was stirred at r.t. for additional 12 h, then treated with sat. aq NH_4Cl. After separation of the aqueous phase, the organic layer was washed with brine and dried (Na_2SO_4). Elimination of the solvent under vacuum gave a crude product which was purified by flash chromatography

(EtOAc/petroleum ether, 0.2:1) to yield **3a** as a pale yellow oil (8.7 g, 80%).

^{1}H NMR: δ = 0.22 (s, 9 H), 1.43 (br s, 9 H), 4.05−4.55 (m, 3 H), 4.90 (br s,1 H), 5.01 (br s,1 H).

^{13}C NMR: δ = −0.9, 23.7, 70.6, 72.0, 73.7, 79.0, 80.4, 81.4, 153.6, 182.5.

Anal. calcd for $C_{14}H_{23}NO_4Si$: C, 56.54; H, 7.79; N, 4.71. Found C, 56.59; H, 7.74; N, 4.70.

(*S*)-4-[3-(Trimethylsilanyl)propynoyl]oxazolidine-3-carboxylic Acid Benzyl Ester (3b)

Compound **3b** was prepared accordingly, starting from **2b** (5.5 g, 18.7 mmol). The crude product obtained was purified by flash chromatography (SiO_2, EtOAc/hexane, 6:4) to give pure **3b** (4.9 g, 80%).

^{1}H NMR (mixture of two conformers): δ = 0.29 (s, 9 H), 4,22 (br s, 2 H), 4.44 (s, 0.6 H), 4.60 (s, 0.4 H), 5.00 (br s, 1 H), 5.07 (br s, 1 H), 5.16 (m, 2 H), 7.34 (m, 5 H).

^{13}C NMR: δ = −0.9, 69.6, 72.0, 73.7, 79.0, 80.4, 81.4, 127.2, 127.5, 128,8, 141.0, 153.6, 182.5

Anal. calcd for $C_{17}H_{21}NO_4Si$: C, 61.60; H, 6.39; N, 4.23. Found C, 61.59; H, 6.34; N, 4.23.

(*S*)-4-[(*E*)-3-(*N*,*N*-Diethylamino)propenoyl]oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (4a); Typical Procedure

A solution of **3a** (1.8 g, 6.1 mmol) was added at 0 °C to a 40% aq solution of Et_2NH (12 mmol). The mixture was stirred at r.t. for 3 h, then extracted with Et_2O. After drying the Et_2O layer (Na_2SO_4) and removal of the solvent gave the pure enamino ketone **4a** (1.6 g, 86%) as a colorless oil.

^{1}H NMR: δ = 1.14 (br t, 6 H), 1.43 (br s, 9 H), 3.23 (br q, 4 H), 3.97 (br m, 1 H), 4.09−4.40 (br m, 2 H), 4.72−5.05 (m, 2 H), 5.16 (d, 1 H, *J* = 12.6 Hz), 7.66 (d, 1 H, *J* = 12.6 Hz).

^{13}C NMR: δ = 13.8, 28.6, 46.0, 70.6, 71.9, 74.5, 80.3, 107.4, 144.0, 157.0, 191.8.

Anal. calcd for $C_{15}H_{26}N_2O_4$: C, 60.38; H, 8.78; N, 9.39. Found C, 60.31; H, 8.74; N, 9.35.

(*S*)-4-[(E)-3-(*N*,*N*-Diethylamino)propenoyl]oxazolidine-3-carboxylic Acid Benzyl Ester (4b)

Compound **4b** was prepared accordingly, starting from **3b** (2.0 g, 6.0 mmol). The crude product obtained was purified by flash chromatography (SiO_2, EtOAc/EtOH, 10:1) to give pure **4b** as an oil (1.8 g, 89%).

^{1}H NMR: δ = 1.03 (br t, 3 H), 1.14 (t, 3 H, *J* = 7.1 Hz), 3.07 (br s, 2 H), 3.22 (q, 2 H, *J* = 7.1 Hz), 4.00 (m, 1 H), 4.16 (br m, 1 H), 4.40 (br m, 1 H), 4.88 (br m, 1 H), 5.10 (m, 4 H), 7.26 (br s, 5 H), 7.61 (br d, 1 H).

^{13}C NMR: δ = 13.8, 46.1, 70.0, 71.8, 74.5, 80.3, 107.2, 127.2, 127.5, 128,8, 141.0, 144.0, 157.0, 191.8.

Anal. calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found C, 65.00; H, 7.32; N, 8.40.

(*S*)-4-[1*H*-Pyrazol-3(5)-yl]oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (5a)

To a solution of **3a** (1.8 g, 6 mmol) and hydrazine sulfate (1.1 g, 8 mmol) in refluxing EtOH was added slowly sat. aq Na_2CO_3 (1.0 g, 9 mmol). The mixture was stirred under reflux for additional 20 h, then diluted with H_2O and extracted with Et_2O. After drying the Et_2O layer (Na_2SO_4) and elimination of the solvent under vacuum a crude product (1 g) was obtained. Purification by flash chromatography (EtOAc/petroleum ether, 7:3) gave pure **5a** (0.8 g, 54%) as an oil.

^{1}H NMR: δ = 1.43 (br s, 9 H), 1.82−2.27 (m, 3 H), 2.26−2.13 (m, 1 H), 3.34−3.61 (m, 2 H, CH_2), 4. 95 (br dd, 0.4 H, CH), 5.02 (br dd, 0.7 H, CH), 6.07 (dd, 1 H, *J* = 1.9 Hz), 7.44 (dd, 1 H, *J* = 1.9 Hz).

^{13}C NMR: δ =: 28.7, 63.5, 69.8, 80.2, 80.9, 106.8, 135.8, 145.3, 154.5.

Anal. calcd for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16; N, 17.56. Found C, 55.19; H, 7.19; N, 17.56.

(*R*)-*tert*-Butoxycarbonylamino[1*H*-pyrazol-3(5)-yl]acetic Acid (7)

p-Toluenesulfonic acid (0.35 g) was added to a solution of **5a** (0.4 g, 1.8 mmol) in anhyd MeOH (60 mL). The mixture was stirred at r.t. for 24 h, then treated with aq sat. $NaHCO_3$ and concentrated in vacuo to eliminate MeOH. The residue was saturated with brine and extracted with EtOAc. The extracts were then washed with brine and dried (Na_2SO_4). Removal of the solvent under vacuum and purification by flash chromatography (SiO_2, EtOAc/petroleum ether, 4:1) gave **6** (61 mg, 15%) as an oil, along with 0.32 g of unreacted **5a**. Compound **6** was characterized by ^{1}H NMR: δ = 1.39 (s, 9 H), 3.15 (br s, 1 H), 3.81−3.99 (dd, 2 H, *J* = 1.9 Hz), 4.89 (br s, 1 H), 5.57−5.60 (br s, 1 H), 6.07 (dd, 1 H, *J* = 1.9 Hz), 7.48 (dd, 1 H, *J* = 1.9 Hz)]. Jones' reagent (45 mL) was added dropwise at 0 °C to a solution of **6** (61 mg) in acetone (20 mL). The mixture was stirred at r.t. for additional 2 h, then diluted with MeOH to destroy excess Jones' reagent. The organic phase was extracted with CH_2Cl_2, the CH_2Cl_2 layer was washed with H_2O and brine and extracted with aq sat. $NaHCO_3$. The organic phase was discarded and the aq $NaHCO_3$ solution was treated with 10% HCl and extracted with EtOAc. The EtOAc layer was dried (Na_2SO_4) and evaporated to give the pure acid **7** (59 mg, 90%).

^{1}H NMR: δ = 1.35 (s, 9 H), 5.95 (s, 1 H), 6.05 (dd, 1 H, *J* = 1.8 Hz), 7.44 (dd, 1 H, *J* = 1.8 Hz), 11.4 (s, 1 H).

^{13}C NMR: δ = 28.8, 62.5, 70.6, 106.3,135.8, 144.8, 154.5, 176.0.

Anal. calcd for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42. Found C, 49.81; H, 6.30; N, 17.41.

(*S*)-4-(1-Phenyl-1*H*-pyrazol-3-yl)oxazolidine-3-carboxylic Acid Benzyl Ester (8); Typical Procedure

To a refluxing solution of compound **3b** (2.0 g, 6.1 mmol) and phenylhydrazine hydrochloride (1.2 g, 8 mmol) in EtOH was added slowly sat. aq of Na_2CO_3 (1.2 g, 11 mmol). The mixture was stirred for additional 20 h, then diluted with H_2O and extracted with Et_2O. After drying the Et_2O layer (Na_2SO_4) and removal of the solvent under vacuum a viscous oil (2.2 g) was obtained. Purification by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether, 0.2.:0.5:1) gave pure **8** (1.1 g, 52%).

^{1}H NMR: δ = 4.24 (br s, 1 H), 4.33 (m, 1 H), 5.08 (br m, 2 H), 5.18 (br m, 3 H), 6.41 (br d, 1 H), 7.10−7.52 (m, 8 H), 7.61−7.66 m, 2 H), 7.84 (d, 1 H, *J* = 1.9 Hz).

^{13}C NMR: δ = 63.8, 69.7, 80.2, 80.9, 108.0, 118.8, 126.0, 127.2, 127.5, 128.6, 128.8, 140.0, 141.0, 151.4, 156.0.

Anal. calcd for $C_{20}H_{23}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found C, 68.73; H, 5.48; N, 12.06.

(*S*)-4-(1-Phenyl-1*H*-pyrazol-5-yl)oxazolidine-3-carboxylic Acid Benzyl Ester (9)

Compound **9** was prepared accordingly, starting from **4b** (2.0 g, 6.1 mmol) in MeOH. A viscous oil (2.5 g) was obtained, which was purified by flash chromatography (SiO_2, EtOAc/CH_2Cl_2/petroleum ether, 0.5:1:1) to give pure **9** (1.5 g, 72%) as an oil.

^{1}H NMR: δ = 3.87 (br s, 1H), 4.11 (br s, 1 H) 5.01−5.09 (br m, 5 H) 6.34 (d, 1H, J = 1.9 Hz), 6.98−7.55 (m, 10 H) 7.52 (d, 1 H, *J* = 1.9 Hz).

^{13}C NMR: δ = 57.2, 69.7, 80.5, 80.9, 108.0, 118.6, 126.0, 127.2, 127.5, 128.5, 137.3, 140.0, 141.0, 143.4, 156.6.

Anal. calcd for $C_{20}H_{23}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found C, 68.77; H, 5.43; N, 11.99.

(*S*)-[2-Hydroxy-1-(1-phenyl-1*H*-pyrazol-3-yl)ethyl]carbamic Acid Benzyl Ester (10)

p-Toluenesulfonic acid (0.92 g) was added to a solution of **8** (0.8 g, 2.2 mmol) in MeOH/H_2O (1:1, 40 mL). The mixture was refluxed for 48 h, then treated with aq sat. $NaHCO_3$ solution and concentrated in vacuo to remove MeOH. The residue was saturated with NaCl and extracted with EtOAc. The combined organic extracts were then washed with brine and dried (Na_2SO_4). Removal of the solvent under vacuum and purification by flash chromatography (SiO_2, EtOAc/petroleum ether, 1:1) gave **10** (0.4 g, 50%), along with 0.32 g of unreacted **8**.

^{1}H NMR: δ = 3.21 (br s, 1 H), 3.95 (br d, 1 H), 4.08 (dd, 1 H, *J* = 12.6 Hz), 5.00 (m, 1 H), 5.15 (s, 2 H), 5.82 (br d, 1 H), 6.46 (d, 1 H, *J* = 1.9 Hz), 7.27−7.40 (m, 6 H), 7.43 (t, 2 H, *J* = 7.2 Hz), 7.62 (d, 2 H, *J* = 7.2 Hz), 7.87 (d, 1 H, *J* = 1.9 Hz).

^{13}C NMR: δ = 56.3, 69.3, 70.8, 108.0, 118.8, 126.0, 127.2, 127.5, 128.6, 128.8, 140.0, 141.0, 151.4, 157.0.

Anal. calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found C, 67.63; H, 5.68; N, 12.36.

(*S*)-[2-Hydroxy-1-(1-phenyl-1*H*-pyrazol-5-yl)ethyl]carbamic Acid Benzyl Ester (11)

p-Toluenesulfonic acid (0.9 g) was added to a solution of **9** (0.8 g, 2.2 mmol) in anhyd MeOH (40 mL). The mixture was then worked up as above. Elimination of the solvent under vacuum and purification by flash chromatography (SiO_2, EtOAc/petroleum ether, 1:1) gave **11** (0.3 g, 35%), along with 0.12 g of unreacted **9**.

^{1}H NMR: δ = 1.89 (br s, 1 H), 3.97 (br d, 1 H), 4.10 (dd, 1 H, *J* = 12.5 Hz), 4.98 (m, 1 H), 5.14 (s, 2 H), 6.03 (br d, 1 H), 6.45 (d, 1 H, *J* = 1.9 Hz), 7.29−7.40 (m, 5 H), 7.43−7.51 (m, 3 H), 7.65 (m, 2 H), 7.87 (d, 1 H, *J* = 1.9 Hz).

^{13}C NMR: δ = 49.3, 69.3, 71.3 108.0, 118.6, 126.0, 127.2, 127.5, 128.5, 137.3, 140.0, 141.0, 143.4, 157.3.

Anal. calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46. Found C, 67.59; H, 5.63; N, 12.39.

(*R*)-*N*-Benzyloxycarbonylamino-(1-phenyl-1*H*-pyrazol-3-yl)acetic Acid (12)

A solution of $KMnO_4$ (1.3 g) in H_2O (25 ml) was added dropwise at 0 °C to a solution of **10** (2.1 g, 6.2 mmol) and Na_2CO_3 (0.1 g) in H_2O (14 mL). The mixture was stirred at r.t. for 12 h, then stirred at 45 °C for additional 1.5 h. The mixture was filtered, extracted with Et_2O, and the aqueous layer was acidified with 10% HCl. The product was extracted with Et_2O, the Et_2O phase was washed with H_2O and brine and dried (Na_2SO_4). Removal of the solvent gave the pure acid **12** (0.8 g, 35%).

^{1}H NMR: δ = 5.02 (br s, 1 H), 5.16 (br s, 2 H), 6.45 (d, 1 H, *J* = 1.9 Hz), 7.31−7.66 (m, 10 H), 7.96 (d, 1 H, *J* = 1.9 Hz) 8.10 (br s, 1 H), 11.3 (s, 1 H).

^{13}C NMR: δ = 62.3, 69.1, 107.5, 118.3, 126.0, 127.0, 127.2, 128.7, 128.8, 139.2, 140.2, 151.6, 157.8, 176.2.

Anal. calcd for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found C, 64.88; H, 4.88; N, 12.01.

(*R*)-*N*-Benzyloxycarbonylamino-(1-phenyl-1*H*-pyrazol-5-yl)acetic Acid (13)

Jones' reagent (3 mL) was added dropwise at 0 °C to a solution of **11** (1.0 g, 3.0 mmol) in acetone (20 mL). The mixture was stirred at 0 °C for additional 4 h, then diluted with MeOH to destroy excess Jones' reagent. The mixture phase was extracted with EtOAc, the combined EtOAc layers were washed with H_2O and brine, and extracted with aq sat $NaHCO_3$ solution. The organic phase was discarded and the aq $NaHCO_3$ solution was treated with 2 N HCl and extracted with EtOAc. The organic phase was dried (Na_2SO_4) and evaporated to give the pure acid **13** (0.16 g, 15%).

^{1}H NMR: δ = 5.02 (br s, 1 H), 5.16 (br s, 2 H), 6.45 (d, 1 H, *J* = 1.9 Hz), 7.31−7.66 (m, 10 H), 7.96 (d, 1 H, *J* = 1.9 Hz), 8.10 (br s, 1 H), 11.3 (s, 1 H).

^{13}C NMR: δ = 55.8, 69.3, 107.9, 118.5, 125.8 127.3, 127.5, 128.7, 129.0, 136.2, 141.2, 143.2, 157.8, 176.0.

Anal. calcd for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found C, 64.92; H, 4.85; N, 12.05.

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