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Synthesis of chiral pyrazoles and isoxazoles as constrained amino acids

Massimo Falorni, Giampaolo Giacomelli * and Anton Mario Spanedda

Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy

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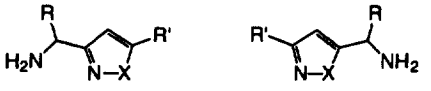
Abstract

A stereospecific syntheses of optically active pyrazoles and isoxazoles from L-proline is described. The procedure presented is based on readily available materials and can be used for preparing new conformationally restricted pyrazole-containing amino acids. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Nonproteinogenic amino acids play an important role in pharmaceutical applications; from this point of view, heteroaryl substituted α-amino acids have been recently considered.[1] A novel and important class of amino acid derived heterocycles is represented by isoxazoles and isothiazoles. During studies on ligands which activate neuronal nicotinic acetylcholine receptors for the palliative treatment for the symptoms of memory loss,[2] a series of novel 3,5-disubstituted isoxazoles and isothiazoles were prepared starting from L-proline, by reacting *N*-Boc-protected-2′-pyrrolidinyl acetylene with a nitrile oxide generated in situ from a nitro precursor.[3,4] The reaction is very convenient but suffers due to the lack of availability of the nitro derivative, moreover the reaction does not occur with nitromethane.

Recently we have become interested in the field of NMDA antagonists;[5] in this context the possibility of preparing amino acids containing heterocycles appeared very attractive.



R = alkyl, COOH,
R' = alkyl, COOH,
X = O, NH, N-Ph

A reliable retrosynthetic analysis for the above compounds suggested the cyclocondensation of an α-acetylenic ketone with a nucleophile such as hydrazine and hydroxylamine derivatives. The reaction is not regioselective in the original procedure,[6] but more recent modifications have shown that the method can be conducted in a highly regioselective manner using silylacetylenic ketones, at least with simple

* Corresponding author. E-mail: ggp@ssmain.uniss.it

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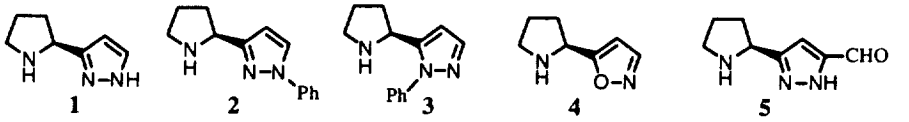
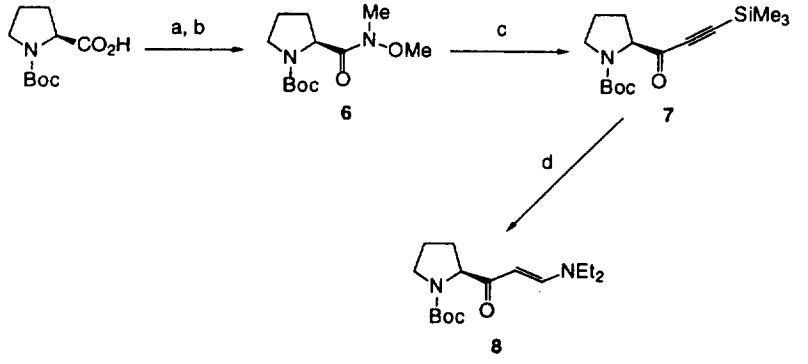
substrates.[7] Therefore, in order to acquire more information about the possibility of using a different method from that reported[3,4] to achieve optically active heterocycle-containing amino acids, we have tested the procedure by using L-proline as the starting amino acid. Here we wish to report the synthesis of optically active 2-pyrazolyl- and 2-isoxazolyl-pyrrolidine derivatives **1–5**.



2. Results and discussion

The preparation of the compounds **1–4** began with the conversion of (*S*)-*N*-*tert*-butoxycarbonyl proline into the corresponding Weinreb prolinamide **6** through reaction with 2 equiv. of *N*,*O*-dimethylhydroxylamine,[8] after treatment with ethyl chloroformate (Scheme 1). The synthesis of (*S*)-1-trimethylsilyl-3-(2′-*N*′-*tert*-butoxycarbonylpirrolidinyl)propin-3-one **7** was performed by reacting (*S*)-*N*-*tert*-butoxycarbonyl-(*N*′-methoxy-*N*′-methyl)prolinamide **6** with trimethylsilylethynyl magnesium bromide. The treatment with Et_2NH provided an efficient and quantitative transformation to (*S*)-(*E*)-1-*N*,*N*-diethylamino-3-(2′-*N*′-*tert*-butoxycarbonylpyrrolidinyl)-propen-3-one **8**.



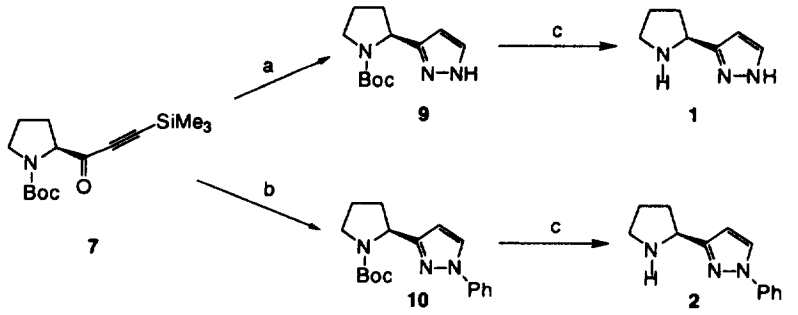
a: $ClCO_2Et$, NMM, CH_2Cl_2, -20°C. b: HON(OMe)Me, 25°C.
c: Me_3Si-C≡C-MgBr, Et_2O, 25°C. d: Et_2NH, EtOH, 25°C, 12h.

Scheme 1.

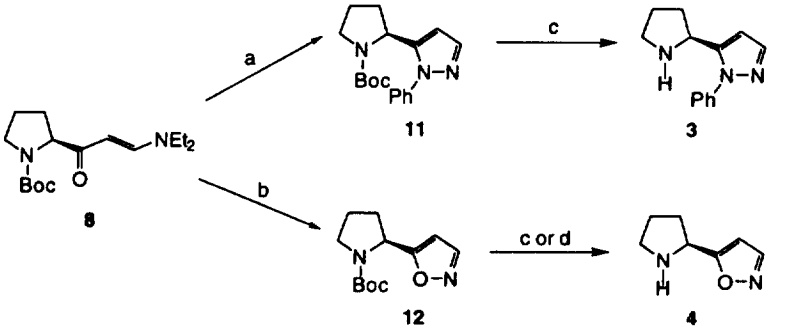
The cyclocondensations were carried out as generally described.[7] The acetylenic ketone **7** was refluxed with an ethanolic solution of 1.5 equiv. of hydrazine sulfate and then treated with a saturated solution of Na_2CO_3 and (2′*S*)-3(5)-(2′-*N*-*tert*-butoxycarbonyl-pyrrolidinyl)pyrazole **9** was isolated in 50% yield after flash-chromatography purification. Using similar conditions, (2′*S*)-1-phenyl-3-(2′-*N*-*tert*-butoxycarbonylpyrrolidinyl)pyrazole **10** was obtained (Scheme 2). The isomeric (2′*S*)-1-phenyl-3-(2′-*N*-*tert*-butoxycarbonylpyrrolidinyl)pyrazole **11** was recovered in 50% yield by refluxing an ethanolic solution of phenylhydrazine with the enamino ketone **8**.

Unfortunately, problems were encountered in the reaction of compounds **7** and **8** with hydroxylamine. Firstly, no isoxazole was formed from the compounds **7**, under various reaction conditions. Secondly, the formation of (2′*S*)-5-(2′-*N*-*tert*-butoxycarbonyl-pyrrolidinyl)isoxazole **12** occurred to a poor extent (35% yield) and all attempts to increase the yield were unsuccessful.

In all cases no trace of the corresponding regioisomer was found in the recovered products. The removal of the protective group by trifluoroacetic acid afforded the compounds **1–4**, which were



a: NH_2NH_2, Na_2CO_3, EtOH, Δ. b: $PhNHNH_2$, Na_2CO_3, EtOH, Δ. c: TFA.

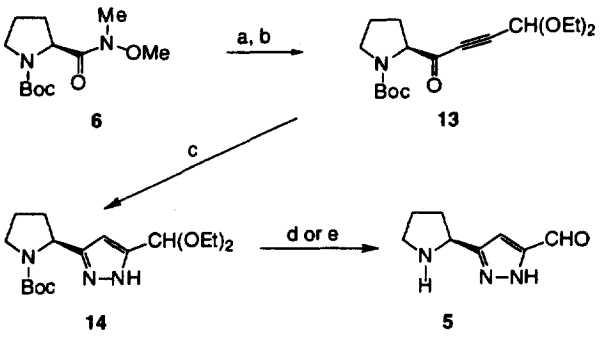


a: $PhNHNH_2$, MeOH, Δ. b: NH_2OH, MeOH, Δ. c: TFA. d: HCl/EtOAc

Scheme 2.

characterized by NMR analysis. The stereochemical course of the cyclocondensation was evaluated by ^{1}H NMR analysis of the diastereoisomeric Mosher amide, prepared by reaction of (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (MPTACl) with (2′*S*)-1-phenyl-5-(2′-pyrrolidinyl)pyrazole **3**. The two diastereomers were found to be clearly distinguishable and consisted of a 95:5 mixture. From these data, an enantiomeric purity of about 90% could be calculated, demonstrating that a small amount of racemization accompanies the cyclocondensation reaction.

Thus, the synthetic protocol we have chosen for preparing chiral optically active heterocyclic systems from L-proline seems to be convenient and versatile, at least for pyrazole substrates. Therefore, in order to obtain information about the applicability of the reaction to more complex systems, we have undertaken the preparation of (2′*S*)-3(5)-formyl-5(3)-(2′-pyrrolidinyl)pyrazole (**5**) as a useful intermediate for the synthesis of new optically active conformationally restricted amino acids, such as 3(5)-alkylamino-5(3)-carboxy pyrazoles, as a valuable tool in the design of peptidomimetics.[9] Thus, a sample of compound **6** was treated with the Grignard reagent from 3,3-dimethoxy-1-propyne in THF to give compound **13**; the next reaction with an ethanolic solution of hydrazine gave (2′*S*)-3(5)-diethoxymethyl-5(3)-(2′-*N*-*tert*-butoxycarbonylpyrrolidinyl)pyrazole **14** in good yield (55%) after purification (Scheme 3). The deprotection of **14** furnished a sample of compound **5**, the structure of which was confirmed by ^{1}H NMR analysis.[10]



a: BrMg—≡—$CH(OEt)_2$, THF, 25°C. b: H_2O, NH_4Cl . c: NH_2NH_2, EtOH,Δ.
d: TFA. e: HCl/EtOAc

Scheme 3.

3. Experimental section

Melting and boiling points are uncorrected. Bulb to bulb distillations were carried out with a Büchi GRK-51 apparatus equipped with a vacuum controller Büchi B-168. Melting points were determined on a microscope Leitz LABORLUX S equipped with Leitz Microscope Heating Stage 350 and are uncorrected. Elemental analyses were performed on a Perkin–Elmer 420 B analyzer. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter in a 1 dm tube. The ^1H NMR (300 MHz), ^{13}C NMR (75.4 MHz) and ^{19}F NMR (282 MHz) Fourier transform spectra were obtained with a Varian VXR-300 spectrometer on $CDCl_3$ solutions (unless otherwise specified). All reactions involving air sensitive materials were carried out under an argon atmosphere; all reagents and solvents employed were reagent grade materials purified by standard methods and distilled before use. As chiral starting material L-proline of '*BioChemica*' grade (chemical and enantiomeric purity >99%) purchased from Fluka Chemie AG was used. L-*N*-Boc-Proline was prepared according to reported procedures. Satisfactory microanalyses were obtained for all unknown compounds: C±0.32%, H±0.40, N±0.16.

*3.1. (S)-*N*-tert-Butoxycarbonyl-(N′-methoxy-N′-methyl)prolinamide, 6*

Under vigorous stirring and at −15°C, 4-methylmorpholine (5.1 mL, 46.3 mmol) in CH_2Cl_2 (20 mL) and ethylchloroformate (8.4 mL, 88.8 mmol) in CH_2Cl_2 (20 mL) were added to (*S*)-*N*-Boc-proline (10 g, 46.3 mmol) in CH_2Cl_2 (60 mL). The reaction 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, 12 h at rt, then treated with water (100 mL). After separation of the organic layer, the aqueous phase was extracted with EtOAc (25 mL) and washed with 10% aq. $NaHCO_3$, sat. aq. NaCl, 5% aq. HCl and sat. aq. NaCl (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:CH_2Cl_2=1:1) yielded **6**, as a colourless oil (9.5 g, 80%); ^1H NMR δ: (mixture of two conformers) 1.38 (s, 4.5H, Boc), 1.43 (s, 4.5H, Boc), 1.70–1.89 (m, 2H), 1.89–2.03 (m, 1H), 2.15 (m, 1H), 3.16 (s, 3H, N–CH_3), 3.32–3.48 (m, 1H), 3.48–3.61 (m, 1H), 3.69 (s, 1.5H, O–CH_3), 3.75 (s, 1.5H, O–CH_3), 4.57 (dd, 0.5H, CH), 4.69 (dd, 0.5H, CH); ^{13}C NMR δ: (mixture of two conformers) 168.3, 143.6, 74.0, 62.4, 61.5, 57.2, 56,8, 47.0, 32.8, 28.7, 23.7.

3.2. (S)-1-Trimethylsilyl-3-(2′-N-tert-butoxycarbonylpyrrolidinyl)propyn-3-one, 7

To a solution of 50 mmol of ethyl magnesium bromide in 50 mL of anhydrous diethyl ether, trimethylsilyl acetylene (4.9 g, 50 mmol) in 20 mL of ether was slowly added under stirring and then heated until formation of a white suspension. The mixture was then kept at 0°C and compound **6** (9.5 g, 36.6 mmol) in 25 mL of anhydrous ether was added over a period of 5 min. The solution was stirred at rt for an additional 12 h, then treated with saturated aq. NH_4Cl. After separation of the organic layer, the aqueous phase 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:CH_2Cl_2=1:3:6) to yield **7** as a yellow crystalline solid (mp 76–77°C, 5.5 g, 60%), $[\alpha]^{25}_D$ −74.9 (c 7, CH_2Cl_2); ^{1}H NMR (mixture of two conformers) 0.22 (s, 9H, –$SiMe_3$), 1.41 (s, 6.3H, Boc), 1.46 (s, 2.7H, Boc), 1.82–2.03 (m, 3H), 2.10–2.30 (m, 1H), 3.43–3.55 (m, 2H), 4.21 (dd, 0.7H, CH), 4.40 (dd, 0.3H, CH); ^{13}C NMR δ: (mixture of two conformers) 182.5, 153.6, 90.3, 80.4, 73.7, 66.6, 66.4, 46.8, 46.5, 30.2, 28.4, 23.7, −0.9.

3.3. (S)-(E)-1-N,N-Diethylamino-3-(2′-N-tert-butoxycarbonylpyrrolidinyl)propen-3-one, 8

A solution of **7** (1.8 g, 6.1 mmol) was added at 0°C to a 40% aq. solution of Et_2NH (12 mmol). The reaction mixture was stirred at room temperature for 3 h, then extracted with diethyl ether. After drying (Na_2SO_4) and removal of the solvent, the oil residue was purified by flash chromatography (EtOAc:acetone:petroleum ether=60:25:15) to give the enamino ketone **8** (1.7 g, 96%) as a pale yellow solid (mp 82–83°C, 5.5 g, 61%), $[\alpha]^{25}_D$ −104 (c 3, CH_2Cl_2); ^{1}H NMR (mixture of two conformers) 1.07–1.29 (broad signal, 6H), 1.39 (s, 6.3H, Boc), 1.43 (s, 2.7H, Boc), 1.78–2.25 (m, 4H), 3.12–3.34 (broad signal, 4H, N–CH_2), 3.35–3.57 (m, 2H), 4. 15 (m, 0.7H, CH), 4.30 (dd, 0.3H, CH), 5.13 (t like, 1H, =CH, J=12.5), 7.65 (d, 1H, =CH, J=12.5); ^{13}C NMR δ: (mixture of two conformers) 191.9, 157.2, 144.0, 107.5, 74.4, 67.8, 47.4, 41.2, 28.9, 24.3, 20.8, 13.2.

3.4. (S)-1,1-Diethoxy-4-(2′-N-tert-butoxycarbonylpyrrolidinyl)but-2-yn-4-one, 13

To a solution of 4 mmol of ethyl magnesium bromide in 10 mL of anhydrous diethyl ether, 3,3-diethoxy-1-propyne (0.58 g, 4.5 mmol) in 20 mL of ether was slowly added under stirring and then heated until formation of a white suspension. The mixture was then kept at 0°C and compound **6** (1.0 g, 3.9 mmol) in 25 mL of anhydrous ether was added. The solution was stirred at rt for additional 20 h, then treated with saturated aq. NH_4Cl. After separation of the organic layer, the aqueous phase 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:CH_2Cl_2=1:3:6) to yield **13** as a pale brown oil (0.3 g, 24%), $[\alpha]^{25}_D$ −51.5 (c 3, CH_2Cl_2); ^{1}H NMR (mixture of two conformers) 1.15 (t, 6H, CH_3–CH_2), 1.33 (s, 6.3H, Boc), 1.38 (s, 2.7H, Boc), 1.74–2.01 (m, 3H), 2.07–2.24 (m, 1H), 3.42–3.58 (m, 4H, CH_3–CH_2), 3.57–3.71 (m, 2H, CH_2), 4.18 (dd, 0.7H, CH), 4.32 (dd, 0.3H, CH), 5.30 (s, 1H, O–CH–O); ^{13}C NMR δ: (mixture of two conformers) 182.0, 131.8, 91.2, 87.7, 80.7, 80.2, 66.9, 66.8, 66.2, 61.7, 46.8, 30.3, 28.4, 23.9, 24.5, 15.2.

3.5. (2′S)-3(5)-(2′-N-tert-Butoxycarbonylpyrrolidinyl)pyrazole, 9

To a solution of compound **7** (1.8 g, 6 mmol) and hydrazine sulphate (1.1 g, 8 mmol) in refluxing ethanol, a saturated aq. solution of Na_2CO_3 (1.0 g, 9 mmol) was added slowly. The mixture was stirred under reflux for an additional 20 h, then diluted with water and extracted with ether. After drying

(Na_2SO_4) and elimination of the solvent under vacuum a crude product (1 g) was obtained: purification by flash chromatography (EtOAc:CH_2Cl_2:acetone=1:2:1) gave pure **9** (0.7 g, 50%), $[\alpha]^{25}_D$ −80.6 (c 4, CH_2Cl_2); ^{1}H NMR (mixture of two conformers) 1.28 (s, 4H, Boc), 1.44 (s, 5H, Boc), 1.82–2.27 (m, 3H), 2.26–2.13 (m, 1H), 3.34–3.61 (m, 2H, CH_2), 4. 95 (broad dd, 0.4H, CH), 5.02 (broad dd, 0.7H, CH), 6.07 (dd, 1H), 7.44 (dd, 1H); ^{13}C NMR δ: 176.4, 153.8, 145.3, 116.8, 69.8, 55.0, 46.6, 31.1, 28.7, 21.3.

3.6. (2′S)-1-Phenyl-3-(2′-N-tert-butoxycarbonylpyrrolidinyl)pyrazole, 10

To a solution of compound **7** (1.8 g, 6.1 mmol) and phenylhydrazine hydrochloride (1.2 g, 8 mmol) in ethanol, kept at reflux, a saturated aq. solution of Na_2CO_3 (1.2 g, 11 mmol) was added slowly. The mixture was stirred for an additional 20 h, then diluted with water and extracted with ether. After drying (Na_2SO_4) and elimination of the solvent under vacuum a crude viscous oil (2 g) was obtained: purification by flash chromatography (EtOAc:CH_2Cl_2:petroleum ether=1.5:1:1) gave pure **10** (0.8 g, 42%), $[\alpha]^{25}_D$ −67.9 (c 4, CH_2Cl_2); ^{1}H NMR (mixture of two conformers) 1.26 (s, 6H, Boc), 1.46 (s, 3H, Boc), 1.85–2.03 (m, 2H), 2.13–2.27 (m, 2H), 3.43–3.61 (m, 2H), 4. 95 (broad dd, 0.6H, CH), 5.03 (broad dd, 0.4H, CH), 6.28 (d, 1H), 7.22 (t, 1H), 7.39 (t, 2H), 7.64 (d, 2H), 7.79 (d, 1H); ^{13}C NMR δ: 154.5, 140.1, 129.2, 126.8, 125.9, 118.7, 113.7, 105.8, 79.1, 55.6, 46.6, 33.8, 28.2, 23.3.

3.7. (2′S)-1-Phenyl-5-(2′-N-tert-butoxycarbonylpyrrolidinyl)pyrazole, 11

A solution of compound **8** (0.5 g, 1.7 mmol) and phenylhydrazine hydrochloride (0.3 g, 2.0 mmol) in methanol was kept at reflux for 7 h, then diluted with water and extracted with ether. After drying (Na_2SO_4) and elimination of the solvent under vacuum a crude viscous oil (0.6 g) was obtained: purification by flash chromatography (EtOAc:CH_2Cl_2:petroleum ether=9:3:10) gave pure **11** (0.2 g, 38%) as a crystalline solid, mp 110–112°C, $[\alpha]^{25}_D$ +9.5 (c 2, CH_2Cl_2); ^{1}H NMR (mixture of two conformers) 1.24 (s, 6H, Boc), 1.44 (s, 3H, Boc), 1.77–2.03 (m, 3H), 2.01–2.21 (m, 1H), 3.30–3.68 (m, 2H), 4.90 (broad dd, 0.6H, CH), 5.14 (broad dd, 0.4H, CH), 6.15 (s, 1H), 7.22–7.51 (m, 5H), 7.64 (s, 1H); ^{13}C NMR δ: 154.5, 139.5, 129.1, 128.1, 125.7, 106.8, 103.9, 90.3, 79.7, 53.5, 46.4, 33.9, 28.2, 22.8.

3.8. (2′S)-5-(2′-N-tert-Butoxycarbonylpyrrolidinyl)isoxazole, 12

A solution of compound **8** (0.7 g, 2.4 mmol) and hydroxylamine hydrochloride (0.18 g, 2.6 mmol) in methanol was kept at reflux for 7 h, then diluted with water and extracted with ether. After drying (Na_2SO_4) and elimination of the solvent under vacuum a crude yellow oil (0.5 g) was obtained: purification by flash chromatography (EtOAc:petroleum ether=7:3) gave pure **12** (0.2 g, 35%), $[\alpha]^{25}_D$ −105 (c 5, CH_2Cl_2); ^{1}H NMR (mixture of two conformers) 1.21 (s, 6H, Boc), 1.32 (s, 3H, Boc), 1.77–2.03 (m, 3H), 2.01–2.21 (m, 1H), 3.30–3.68 (m, 2H), 4.90 (broad dd, 0.6H, CH), 5.14 (broad dd, 0.4H, CH), 6.15 (s, 1H), 7.22–7.51 (m, 5H), 7.64 (s, 1H); ^{13}C NMR δ: 154.5, 139.5, 129.1, 128.1, 125.7, 106.8, 103.9, 90.3, 79.7, 53.5, 46.4, 33.9, 28.2, 22.8.

3.9. (2′S)-3(5)-(2′-N-tert-Butoxycarbonyl-pyrrolidinyl)-5(3)-(1,1-diethoxymethyl) pyrazole, 14

The compound **14** was prepared following the procedure described for **9**, starting from **13** (0.27 g, 0.83 mmol). The crude product obtained was purified by flash chromatography (EtOAc:CH_2Cl_2=2:1) to give pure **14** (mp 159–161°C, 0.2 g, 78%), $[\alpha]^{25}_D$ −158 (c 3, CH_2Cl_2); ^{1}H NMR (mixture of two conformers) 1.12 (t, 6H, CH_3), 1.22 (s, 6H, Boc), 1.35 (s, 3H, Boc), 1.72–1.98 (m, 3H), 2.02–2.17 (m, 1H), 3.24–3.34

(m, 1H), 3.38–3.64 (m, 5H), 4. 81 (dd, 0.4H, CH), 4.88 (dd, 0.7H, CH), 5.49 (d, 1H), 6.06 (d, 1H); ^{13}C NMR δ: 176.4, 153.8, 101.8, 98.7, 81.1, 55.8, 52.3, 47.3, 30.4, 28.8, 24.9, 15.2.

3.10. Deprotection of compounds 1–5: general procedure

(a): To a solution of 0.57 mmol of Boc-protected substrate (**1–5**) in 5 mL of CH_2Cl_2, 2 mL of trifluoroacetic acid were added at 0°C. The mixture was stirred for an additional hour at 0°C and then concentrated in vacuo. The residue was washed with saturated $NaHCO_3$ and continuously extracted with CH_2Cl_2. After solvent evaporation, the residue was purified by flash chromatography to give the following pure compound.

3.10.1. (2′S)-3(5)-(2′-Pyrrolidinyl)pyrazole, 1

37% Yield, $[\alpha]^{25}_D$ −21.9 (c 1, $CHCl_3$); ^1H NMR 1.81–2.18 (m, 3H), 2.26–2.46 (m, 1H), 3.26–3.52 (m, 2H, CH_2), 4. 80 (m, 1H, CH), 6.21 (d, 1H), 6.92 (broad s, 2H, NH), 7.54 (d, 1H); ^{13}C NMR δ: 144.3, 126.8, 105.3, 57.2, 44.6, 32.2, 22.1.

3.10.2. (2′S)-1-Phenyl-3-(2′-pyrrolidinyl)pyrazole, 2

57% Yield, $[\alpha]^{25}_D$ −31.1 (c 2, CH_2Cl_2); ^1H NMR 2.10 (m, 2H), 2.29 (m, 1H), 2.41 (m, 1H), 3.48 (m, 2H), 4.82 (dd, 1H, CH), 6.60 (d, 1H, J=2.5), 6.78 (broad s, 1H, NH), 7.27 (t, 1H), 7.43 (t, 2H), 7.65 (d, 2H), 7.83 (d, 1H, J=2.5); ^{13}C NMR δ: 140.1, 129.2, 126.8, 125.3, 108.6, 113.7, 105.8, 57.6, 44.6, 32.2, 23.1.

3.10.3. (2′S)-1-Phenyl-5-(2′-pyrrolidinyl)pyrazole, 3

Mp 144°C, 91% yield, $[\alpha]^{25}_D$ +39.1 (c 2, CH_2Cl_2); ^1H NMR 1.94–2.35 (m, 4H), 3.18 (m, 1H, CH_2), 3.37 (m, 1H, CH_2), 4.56 (dd, 1H, CH), 4.96 (broad s, 1H, NH), 6.68 (d, 1H, J=2.5), 7.38 (t, 2H), 7.44 (t, 2H), 7.46 (d, 1H), 7.63 (d, 1H, J=2.5); ^{13}C NMR δ: 140.8, 139.8, 137.8, 129.9, 126.2, 118.9, 106.6, 54.6, 45.4, 33.1, 23.9.

(b): A sample of product (5 mmol) was dissolved in 5 mL of EtOAc; to this solution 4.5 N HCl in EtOAc (17 mL) was rapidly added under magnetic stirring and slowly a precipitate was formed. After 30 min the solvent was removed in vacuo (0.01 mbar) affording the pure compound as hydrochloride, which was purified by washing with petroleum ether. The pure compound can be obtained by washing the hydrochloride with saturated $NaHCO_3$ and continuously extracting with CH_2Cl_2.

3.10.4. (2′S)-5-(2′-Pyrrolidinyl)isoxazole, 4

From (a): 31% yield; ^1H NMR 1.80 (m, 3H), 2.10 (m, 1H), 3.01 (m, 2H), 4.29 (dd, 1H, CH), 6.04 (s, 1H), 8.06 (s, 1H): from (b) as hydrochloride (mp 137–139°C, 82% yield), $[\alpha]^{25}_D$ +5.8 (c 2, H_2O); ^1H NMR (D_2O) 2.19 (m, 3H), 2.54 (m, 1H), 3.48 (m, 2H), 5.01 (dd, 1H, CH), 6.64 (s, 1H), 8.46 (s, 1H); ^{13}C NMR δ: 162.2, 148.5, 101.1, 50.8, 42.8, 25.6, 20.1.

3.10.5. (2′S)-3(5)-Formyl-5(3)-(2′-pyrrolidinyl)pyrazole, 5

From (a): 18% yield; ^1H NMR (DMSO-d_6) 1.98–2.09 (m, 3H), 2.38–2.47 (m, 1H), 3.46–3.57 (m, 2H), 5.14 (dd, 1H, CH), 5.79 (s, 1H), 8.34 (s, 1H, CHO): from (b) as hydrochloride (mp 180°C (dec), 86% yield) $[\alpha]^{25}_D$ +7.4 (c 0.5, H_2O); ^1H NMR (D_2O) 2.22–2.45 (m, 3H), 2.54–2.72 (m, 1H), 3.58 (m, 2H), 4.96 (dd, 1H, CH), 6.90 (s, 1H), 9.93 (s, 1H); ^{13}C NMR δ: 182.0, 146.5, 135.7, 105.2, 53.6, 42.4, 26.6, 20.1.

3.11. Determination of the ee

A sample of **3** (70 mg, 0.33 mmol) and distilled (+)-MPTACl (0.1 g, 0.4 mmol) were mixed with CH_2Cl_2 and dry pyridine (1 mL) at 0°C and allowed to stand for 48 h at rt. Water was added and the mixture extracted with diethyl ether. The ethereal phase was washed successively with sat. aq. Na_2CO_3, water and dried (Na_2SO_4). After removal of the solvent in vacuo the residual 1-phenyl-5-[1′-(α-methoxy-α-trifluoromethylphenylacetyl)-2′-pyrrolidinyl]pyrazole was analyzed by ^1H NMR and ^{19}F NMR.

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References

1. (a) Begtrup, M.; Sløk, F. A. *Synthesis*, **1993**, 861; (b) Amici, R.; Pevarello, P.; Colombo, M.; Varasi, M. *Synthesis*, **1996**, 1177.
2. (a) Ebert, B.; Lenz, S.; Brehm, L.; Bregnedal, P.; Hansen, J. J.; Frederiksen, K.; Bøgesø, K. P.; Krogsgaard-Larsen, P. *J. Med. Chem.*, **1994**, *37*, 878; (b) Johansen, T. N.; Frydenvang, K.; Ebert, B.; Krogsgaard-Larsen, P.; Madsen, U. *J. Med. Chem.*, **1994**, *37*, 3252; (c) Madsen, U.; Bang-Andersen, B.; Brehm, L.; Christensen, I. T.; Ebert, B.; Kristoffersen, I. T. S.; Lang, Y.; Krogsgaard-Larsen, P. *J. Med. Chem.*, **1996**, *39*, 1682.
3. Garvey, D. S.; Wasicak, J. T.; Decker, M. W.; Brioni, J. D.; Buckley, M. J.; Sullivan, J. P.; Carrera, G. M.; Holladay, M. W.; Arneric, S. P.; Williams, M. *J. Med. Chem.*, **1994**, *37*, 1055.
4. Garney, D. S.; Wasicak, J. T.; Elliot, R. L.; Lebold, R. L.; Hettinger, A.; Carrera, G. M.; Lin, N.; He, Y.; Holladay, M. W.; Anderson, D. J.; Cadman, E. D.; Raszkiewicz, J. L.; Sullivan, J. P.; Arneric, S. P. *J. Med. Chem.*, **1994**, *37*, 4455.
5. Falorni, M.; Giacomelli, G. *Synlett*, **1996**, 143.
6. Wakefield, B. G.; Wright, D. J. *Adv. Heterocycl. Chem.*, **1979**, *25*, 147.
7. (a) Giacomelli, G.; Rosini, C.; Caporusso, A. M.; Palla, F. *J. Org. Chem.*, **1983**, *48*, 4887; (b) Falorni, M.; Lardicci, L.; Giacomelli, G. *Gazz. Chim. Ital.*, **1987**, *117*, 7.
8. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.*, **1981**, *39*, 3815.
9. Falorni, M.; Dettori, G.; Giacomelli, G. *Tetrahedron: Asymmetry*, **1998**, *9*, 1419.
10. The aldehyde can be stored under argon or as hydrochloride. When in solvent, the free aldehyde undergoes slow decomposition.