Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 1347–1354

Chiral imidazole derivatives synthesis from enantiopure *N*-protected α-amino acids

Filip Bureš* and Jiří Kulhánek

Department of Organic Chemistry, University of Pardubice, nám. Čs. Legií 565, Pardubice 53210, Czech Republic

Received 21 December 2004; accepted 21 January 2005

Abstract—A route to the preparation of enantiopure ligands based on a 2-phenylimidazol ring is described. The stereogenic centre is placed into the chain bonded to the fourth carbon of the imidazole ring. The synthesis starts from inexpensive and readily available *N*-protected α-amino acids, as the source of chirality, which are converted into appropriate α-diazoketones and, consequently, into α-bromoketones. These α-bromoketones are good precursors for reactions with amidines to provide the imidazole ring. The deprotection into the final products was carried out using hydrogen.

1. Introduction

Enantiopure imidazole derivatives are very important ligands in the chemistry of metal complexes. For that reason, we wanted to synthesize several chiral derivatives of 2-phenylimidazole substituted at the 4-position. The chain at the 4-position is a source of chirality; the imidazole ring performs as the complexation molecule part while the phenyl ring can be modified with suitable groups to support the required properties.

In the literature it is possible to find some methods describing the preparation of similar compounds. McKervey and co-workers[1–3] describe the preparation from *N*-CBz α-amino acids that were converted into appropriate α-diazoketones. The oxidation of the diazo group using DMD (dimethyldioxirane) acetone solution provides α-oxoaldehydes that are allowed to condense with benzaldehyde in the presence of ammonium acetate into 2-phenylimidazole derivatives. The key step of the synthesis is the oxidation of α-diazoketone. The reaction is finished in 10 min at room temperature (followed on TLC), resulting in a solution of α-oxoaldehydes in acetone.

Balenovic and Bregant[4,5] and Borkovec et al.[6] describe the transformation of *N*-phthaloylated α-diazoketones into α-oxoaldehydes using nitrones. In the first step, the α-diazoketone is transformed into an α-bromoketone using hydrobromic acid in glacial acetic acid, then activated with pyridine and, consequently, the reaction with *p*-nitroso-*N*,*N*-dimethylaniline provides nitrone, which is then decomposed into α-oxoaldehyde using diluted sulfuric acid.

The preparation of our derivatives starts from inexpensive and readily available *N*-CBz α-amino acids **1**, which were transformed into α-diazoketones **2** via a mixed anhydride by treatment with ethereal diazomethane. The α-diazoketones react with hydrobromic acid to provide α-bromoketones **3** as in Scheme 1. The next step of the synthesis is the reaction of α-bromoketones with benzamidine hydrochloride in a THF/water/K_2CO_3 system[7] to afford the CBz-imidazole derivatives **4**. The deprotection into the final enantiopure imidazole **5** is carried out using hydrogen (Scheme 2).

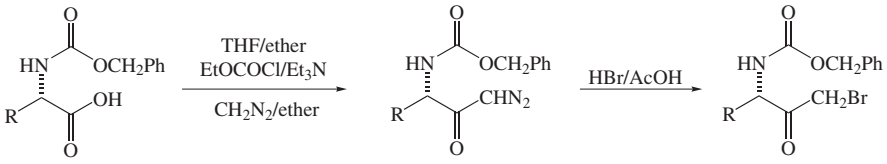
2. Results and discussion

A series of reactions using either the DMD or nitrone method were conducted, and from these experiments, we made a number of observations.

The disadvantage of the DMD method is the preparation of an oxidation agent (DMD) from Oxone® (Aldrich) in really poor yield (less than 5%), and the structures of the α-oxoaldehydes were not satisfactorily

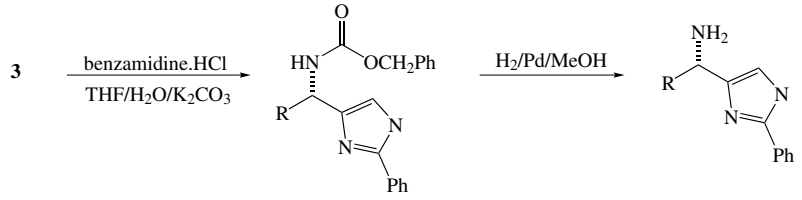
* Corresponding author. Tel.: +42 0466037018; fax: +42 0466037068; e-mail: filip.bures@upce.cz

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.01.049



1 2 3

Scheme 1.



4 5

Scheme 2.

explained, either. There is no possible oxidation in bigger scale for safety reasons (explosive DMD).

In the case of the nitrone-transformation and the CBz (benzyloxycarbonyl) protecting group, we observed racemization during the nitrone preparation (using sodium hydroxide as base). Further disadvantages are the poor total yield and that a long time is required for the consuming method, which uses toxic *p*-nitroso-*N*,*N*-dimethylaniline.

As starting material, α-diazoketones are optimal. It is not necessary to oxidize them into α-oxoaldehydes, although transformation into α-bromoketones is preferable. α-Bromoketones are reactive species for condensation with amidines. The reaction is carried out in THF at reflux while a water solution of potassium bicarbonate is used as the hydrobromic acid scavenger and liberator of free benzamidine base. Comparing our and the DMD methods (for derivative **4d**), we observed a better yield (89% vs 71%). The final CBz group removal proved very simple.

3. Conclusion

We have developed a route to the preparation of the chiral derivatives of 2,4-disubstituted imidazole from enantiopure amino acid. Following this route we have synthetized seven CBz protected derivatives and, consequently, seven deprotected enantiopure derivatives of 2-phenylimidazole. Some of the properties of the prepared compounds are summarized in Tables 1 and 2. The yields of the condensation reaction varied from moderate {entry **4f**—derivative from (*S*)-isoleucine} to satisfactory (all other entries). Enantiomeric purity was proven from the starting amino acid. Derivatives derived from alanine were prepared in both configurations. All other properties are given in the Experimental at appropriate compounds. Most of the CBz protected derivatives showed in the NMR spectra, hindered rotation at the carbamic acid function.

The molecular weights (MWs) of all the studied compounds were unambiguously identified on the basis of complementary information obtained from the positive-ion mode (i.e., $[M+H]^+$) and the negative-ion mode (i.e., $[M-H]^-$) APCI mass spectra. In addition to the MW determination, tandem mass spectra in both polarity modes provided characteristic neutral losses for some functional groups, for example, $CH_3C_6H_5$ ($\Delta m/z$ 92), $HOCH_2C_6H_5$ (108), $HCOOCH_2C_6H_5$ (136), NH_2-$COOCH_2C_6H_5$ (151), butene (56) or butane (58), propane (44) or propene (42) and $NH_2CH{=}CHC_6H_5$ (119). All observed fragment ions are in accordance with the suggested structures. Compounds **5a**–**f** fragment so easily that the ions corresponding the neutral loss of ammonia are the base peaks in the first-order APCI

Table 1. CBz derivatives **4** preparation

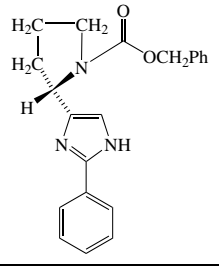
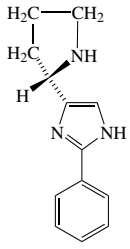
Compd.	Structure	Yield (%)	Ee (%)/conf.	$[\alpha]_D^{20}$ (*c* 1, MeOH)
4a	R = –CH_3	89	99 (*S*)	−25.4
4b	R = –CH_3	85	99 (*R*)	+24.9
4c	R = –$CH(CH_3)_2$	76	99 (*S*)	−45.2
4d	R = –CH_2Ph	65	99 (*S*)	−13.5 (*c* 1, $CHCl_3$)
4e	R = –$CH_2CH(CH_3)_2$	88	99 (*S*)	−48.7
4f	R = –$CH(CH_3)CH_2CH_3$	42	99 (*S*)	−50.2
4g		70	99 (*S*)	−34.2

Table 2. Deprotection into the final products **5**

Compd.	Structure	Yield (%)	Ee (%)/conf.	$[\alpha]_D^{20}$ (*c* 1, MeOH)
5a	R = –CH_3	99	99 (*S*)	+4.1
5b	R = –CH_3	99	99 (*R*)	−4.0
5c	R = –$CH(CH_3)_2$	99	99 (*S*)	+2.7
5d	R = –CH_2Ph	99	99 (*S*)	+23.9
5e	R = –$CH_2CH(CH_3)_2$	99	99 (*S*)	+2.6
5f	R = –$CH(CH_3)CH_2CH_3$	99	99 (*S*)	+4.5
5g		99	99 (*S*)	+12.1

mass spectra in both polarity modes, that is, $[M+H-NH_3]^+$ or $[M-H-NH_3]^-$.

4. Experimental

^1H NMR spectra were recorded in $CDCl_3$ or DMSO at 500 or 360 MHz with Bruker AVANCE 500 or AMX 360 instruments. The ^{13}C spectra were recorded in $CDCl_3$ or DMSO at 125 MHz on a Bruker AVANCE 500 or at 90 MHz with AMX 360 instrument. NMR techniques such as COSY, HMBC and HMQC were used. Chemical shifts are reported in ppm with residual $CHCl_3$ (7.25 ppm), DMSO (2.55) and $CDCl_3$ (77.23 ppm), DMSO (39.51) as references. *J* values are given in hertz.

The positive-ion and negative-ion APCI mass spectra were measured on Esquire 3000 ion trap analyzer (Bruker Daltonics, Bremen, Germany) within the mass range *m*/*z* = 50–1000. Samples were dissolved in acetonitrile and analyzed by direct infusion at a flow rate of 40 μL/min. The ion source temperature was 300 °C, the APCI probe temperature was 350 °C, the flow rate and the pressure of nitrogen were 3 L/min and 25 psi, respectively. The tuning of the mass spectrometer was optimized for the target mass *m*/*z* 300. For MS/MS measurements, the isolation width of precursor ions was 4 *m*/*z*, and the collision amplitude was 0.9 V in all cases.

Optical rotations were measured on Perkin–Elmer 341 instrument, concentration *c* is given in g/100 mL. The diazomethane solution was prepared from *N*-nitroso-*N*-methylurea. The deprotections were carried out in an ROTH pressure vessel.

4.1. α-Diazoketone preparation (general method)

The *N*-protected α-amino acid (27.0 mmol) in dry ether (60 mL) and THF (60 mL) was stirred under argon at −25 °C. Triethylamine (27.0 mmol; 3.8 mL) and ethylchloroformate (27.0 mmol, 2.6 mL) were added to this solution. The solution was stirred for further 30 min, the temperature then allowed to reach −10 °C and the diazomethane solution in ether (2–3 equiv) was added dropwise. The suspension was stirred for an additional 3 h and allowed to reach ambient temperature. The triethylamine hydrochloride was then filtered off and the filtrate was evaporated to half of its original volume. The resulting solution was washed with saturated aqueous sodium hydrogen carbonate (50 mL) and brine (50 mL). The organic layer was dried and evaporated to give a crude product, which was purified by crystallization (dichloromethane–hexane) or on silica gel (ethyl acetate–hexane 1:1).

4.1.1. (3-Diazo-1-(*S*)-methyl-2-oxopropyl)carbamic acid benzyl ester 2a. Prepared from **1a** by the general method to give title compound **2a** as pale yellow needles, yield 96%, mp 89–90 °C, $[\alpha]_D^{20} = -59.1$ (*c* 1, MeOH). Found: C 58.1; H 5.2; N 17.1. $C_{12}H_{13}N_3O_3$ requires C 58.3; H 5.3; N 17.0. ^1H NMR (δ/ppm, 500 MHz, $CDCl_3$) 1.30 (3H, d, *J* = 7.1, C*H*$_3$), 4.11 + 4.24 (1H, m, CBzNHC*H*), 5.06 (2H, 2d, *J* = 12.4, PhC*H*CO), 5.40 (1H, br s, C*H*N_2), 5.52 + 5.61 (1H, br s, CBzN*H*CH), 7.26–7.33 (5H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, $CDCl_3$) 18.5, 53.7, 54.5, 67.1, 128.2, 128.3, 128.6, 136.4, 155.9, 194.1.

4.1.2. (3-Diazo-1-(*R*)-methyl-2-oxopropyl)carbamic acid benzyl ester 2b. Prepared from **1b** by the general method to give title compound **2b** as pale yellow needles, yield 90%, mp 77–79 °C, $[\alpha]_D^{20} = -58.8$ (*c* 1, MeOH). Found: C 58.1; H 5.2; N 17.1. $C_{12}H_{13}N_3O_3$ requires C 58.3; H 5.3; N 17.0. ^1H NMR (δ/ppm, 500 MHz, $CDCl_3$) 1.30 (3H, d, *J* = 7.1, C*H*$_3$), 4.11 + 4.24 (1H, m, CBzNHC*H*), 5.06 (2H, 2d, *J* = 12.4, PhCH_2CO), 5.40 (1H, br s, C*H*N_2), 5.52 + 5.61 (1H, br s, CBzN*H*), 7.26–7.33 (5H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, $CDCl_3$) 18.5, 53.7, 54.5, 67.1, 128.2, 128.3, 128.6, 136.4, 155.9, 194.1.

4.1.3. (3-Diazo-1-(*S*)-(1-methylethyl)-2-oxopropyl)carbamic acid benzyl ester 2c. Prepared from **1c** by the general method to give the title compound **2c** as pale yellow needles, yield 93%, mp 30–31 °C, $[\alpha]_D^{20} = -31.5$ (*c* 1, MeOH). Found: C 61.0; H 6.2; N 15.1. $C_{14}H_{17}N_3O_3$ requires C 61.1; H 6.2; N 15.3. ^1H NMR (δ/ppm, 360 MHz, $CDCl_3$) 0.84 (3H, d, *J* = 6.8, C*H*$_3$), 0.94 (3H, d, *J* = 6.8, C*H*$_3$), 2.04 (1H, m, C*H*$(CH_3)_2$) 3.95 + 4.10 (1H, m, CBzNHC*H*), 5.06 (2H, m, PhCH_2CO), 5.39 (1H, br s, C*H*N_2), 5.59 (1H, d, *J* = 8.8, CBzN*H*), 7.23–7.36 (5H, m, Ar*H*). ^{13}C NMR (δ/ppm, 90 MHz, $CDCl_3$) 17.4, 19.5, 31.2, 54.8, 63.0, 67.1, 128.1, 128.2, 128.6, 136.3, 156.5, 193.6.

4.1.4. (3-Diazo-1-(*S*)-benzyl-2-oxopropyl)carbamic acid benzyl ester 2d. Prepared from **1d** by the general method to give title compound **2d** as a pale yellow solid, yield 98%, mp 80–81 °C, $[\alpha]_D^{20} = -42.1$ (*c* 1, MeOH). Found: C 66.7; H 5.3; N 12.9. $C_{18}H_{17}N_3O_3$ requires C 66.9; H 5.3; N 13.0. ^1H NMR (δ/ppm, 360 MHz, $CDCl_3$) 3.05 (2H, d, *J* = 6.7, PhCH_2CH), 4.50 (1H, m, CBzNHC*H*), 5.09 (2H, m, PhCH_2CO), 5.22 (1H, br s, C*H*N_2), 5.40 (1H, br s, CBzN*H*), 7.18–7.36 (10H, m, Ar*H*). ^{13}C

NMR (δ/ppm, 90 MHz, $CDCl_3$) 38.3, 54.4, 58.7, 66.9, 127.0, 127.9, 128.1, 128.4, 128.5, 129.2, 135.9, 136.0, 155.6, 192.6.

4.1.5. (3-Diazo-1-(*S*)-(2-methylpropyl)-2-oxopropyl)carbamic acid benzyl ester 2e. Prepared from **1e** by the general method to give title compound **2e** as pale yellow needles, yield 91%, mp 64–65 °C, $[\alpha]_D^{20} = -53.6$ (*c* 1, MeOH). Found: C 62.0; H 6.5; N 14.3. $C_{15}H_{19}N_3O_3$ requires C 62.3; H 6.6; N 14.5. ^{1}H NMR (δ/ppm, 500 MHz, $CDCl_3$) 0.91 + 0.92 (6H, 2 × d, *J* = 6.3, 2 × C*H*$_3$), 1.45 + 1.53 (2H, m, C*H*$_2$CH(CH$_3$)$_2$), 1.95 (1H, m, CH$_2$C*H*(CH$_3$)$_2$), 4.12 + 4.24 (1H, m, CBzNHC*H*), 5.07 (2H, m, PhC*H*$_2$CO), 5.43 (1H, br s, C*H*N$_2$), 5.46 (1H, br s, CBzN*H*), 7.29–7.33 (5H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, $CDCl_3$) 21.9, 23.2, 24.8, 41.5, 54.0, 56.5, 67.1, 128.2, 128.3, 128.6, 136.4, 156.2, 194.4.

4.1.6. (3-Diazo-1-(*S*)-(1-methylpropyl)-2-oxopropyl)carbamic acid benzyl ester 2f. Prepared from **1f** by the general method to give title compound **2f** as pale yellow needles, yield 89%, mp 63–64 °C, $[\alpha]_D^{20} = -42.1$ (*c* 1, MeOH). Found: C 61.9.; H 6.4; N 14.2. $C_{15}H_{19}N_3O_3$ requires C 62.3; H 6.6; N 14.5. ^{1}H NMR (δ/ppm, 500 MHz, $CDCl_3$) 0.87 (3H, t, *J* = 7.4, CH$_2$C*H*$_3$), 0.92 (3H, d, *J* = 6.8, CHC*H*$_3$), 1.08 + 1.41 (2H, 2 × m, CH$_3$C*H*$_2$), 1.81 (1H, m, CH$_3$C*H*CH$_2$CH$_3$), 4.01 + 4.13 (1H, m, C*H*NHCBz), 5.08 (2H, m, PhC*H*$_2$CO), 5.40 (1H, br s, C*H*N$_2$), 5.50 (1H, d, *J* = 8.8, CBzN*H*), 7.26–7.34 (5H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, $CDCl_3$) 11.6, 15.8, 24.7, 37.8, 55.0, 62.5, 67.2, 128.2, 128.3, 128.7, 136.4, 156.4, 193.6.

4.1.7. 2-(*S*)-(2-Diazo-1-oxoethyl)pyrrolidine-1-carboxylic acid benzyl ester 2g. Prepared from **1g** by the general method to give the title compound **2g** as a yellow oil, yield 93%, $[\alpha]_D^{20} = -94.4$ (*c* 1, MeOH). Found: C 61.2; H 5.4; N 15.1. $C_{14}H_{15}N_3O_3$ requires C 61.5; H 5.5; N 15.4. ^{1}H NMR (δ/ppm, 360 MHz, $CDCl_3$) 1.84 (2H, m, CH$_2$C*H*$_2$CH$_2$), 2.04 (2H, m, CHC*H*$_2$CH$_2$), 3.52 (2H, m, CH$_2$C*H*$_2$N), 4.29 (1H, m, CH$_2$C*H*N), 5.12 (2H, 2 × d, *J* = 12.6, PhC*H*$_2$CO), 5.25 + 5.46 (1H, br s, C*H*N$_2$), 7.25–7.33 (5H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, $CDCl_3$) 23.6 + 24.4, 29.7 + 31.2, 46.9 + 47.4, 52.7 + 53.3, 64.0, 67.2, 127.7, 127.9, 128.1, 128.4, 128.5, 136.4 + 136.6, 154.5 + 155.3, 194.5 + 195.3.

4.2. α-Bromoketone preparation (general method)

To a solution of α-diazoketone **2** (20.0 mmol) in glacial acetic acid (50 mL), 48% hydrobromic acid (7 mL) was added dropwise with stirring. After stirring for 1 h the reaction mixture was poured on the ice and the precipitate collected or extracted with dichloromethane and washed with water. Crystallization from ether-pet. ether gave the pure product.

4.2.1. (3-Bromo-1-(*S*)-methyl-2-oxopropyl)carbamic acid benzyl ester 3a. Prepared from **2a** by the general method to give the title compound **3a** as a white solid, yield 98%, mp 82–83 °C, $[\alpha]_D^{20} = -33.7$ (*c* 1, MeOH). Found: C 47.9; H 4.6; N 4.5.1, Br 26.4. $C_{12}H_{14}BrNO_3$ requires C 48.0; H 4.7; N 4.7, Br 26.6. ^{1}H NMR (δ/ppm, 500 MHz, $CDCl_3$) 1.38 (3H, d, *J* = 7.1, C*H*$_3$), 4.02 (2H, 2 × d, *J* = 13.0, C*H*$_2$Br), 4.63 (1H, m, CBzNHC*H*), 5.07 (2H, 2 × d, PhC*H*$_2$CO), 5.41 + 5.49 (1H, br s, CBzN*H*), 7.31–7.33 (5H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, $CDCl_3$) 18.0, 31.6, 53.8, 67.3, 128.3, 128.5, 128.7, 136.2, 155.9, 201.3.

4.2.2. (3-Bromo-1-(*R*)-methyl-2-oxopropyl)carbamic acid benzyl ester 3b. Prepared from **2b** by the general method to give the title compound **3b** as a white solid, yield 97%, mp 78–79 °C, $[\alpha]_D^{20} = +33.2$ (*c* 1, MeOH). Found: C 47.9; H 4.6; N 4.2, Br 26.2. $C_{12}H_{14}BrNO_3$ requires C 48.0; H 4.7; N 4.7, Br 26.6. ^{1}H NMR (δ/ppm, 500 MHz, $CDCl_3$) 1.38 (3H, d, *J* = 7.1, C*H*$_3$), 4.02 (2H, 2 × d, *J* = 13.0, CH$_2$Br), 4.63 (1H, m, CBzNHC*H*), 5.07 (2H, 2 × d, PhC*H*$_2$CO), 5.41 + 5.49 (1H, br s, CBzN*H*), 7.31–7.33 (5H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, $CDCl_3$) 18.0, 31.6, 53.8, 67.3, 128.3, 128.5, 128.7, 136.2, 155.9, 201.3.

4.2.3. (3-Bromo-1-(*S*)-(1-methylethyl)-2-oxopropyl)carbamic acid benzyl ester 3c. Prepared from **2c** by the general method to give title compound **3c** as a white solid, yield 98%, mp 74–75 °C, $[\alpha]_D^{20} = -22.5$ (*c* 1, MeOH). Found: C 51.0; H 5.6; N 4.2, Br 24.6. $C_{14}H_{18}BrNO_3$ requires C 51.2; H 5.5; N 4.3, Br 24.4. ^{1}H NMR (δ/ppm, 500 MHz, $CDCl_3$) 0.82 (3H, d, *J* = 6.5, C*H*$_3$), 1.00 (3H, d, *J* = 6.5, C*H*$_3$), 2.20 (1H, m, C*H*(CH$_3$)$_2$), 4.04 (2H, 2 × d, *J* = 13.5, C*H*$_2$Br), 4.57 (1H, k, *J* = 5.0, CBzNHC*H*), 5.09 (2H, 2 × d, *J* = 12.0, PhC*H*$_2$CO), 5.50 (1H, d, *J* = 8.5, CBzN*H*), 7.27–7.37 (5H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, $CDCl_3$) 17.0, 19.8, 30.2, 33.1, 63.0, 67.3, 128.2, 128.6, 129.1, 136.1, 156.5, 200.8.

4.2.4. (3-Bromo-1-(*S*)-benzyl-2-oxopropyl)carbamic acid benzyl ester 3d. Prepared from **2d** by the general method to give title compound **3d** as a white solid, yield 99%, mp 102–103 °C, $[\alpha]_D^{20} = -45.9$ (*c* 1, MeOH). Found: C 57.4; H 4.8; N 3.6, Br 21.0. $C_{18}H_{18}BrNO_3$ requires C 57.5; H 4.8; N 3.7, Br 21.2. ^{1}H NMR (δ/ppm, 360 MHz, $CDCl_3$) 3.12 (2H, m, *J* = 7.0, PhC*H*$_2$CH), 3.89 (2H, 2 × d, *J* = 13.6, C*H*$_2$Br), 4.87 (1H, k, *J* = 7.2, CBzNHC*H*), 5.10 (2H, 2 × d, *J* = 12.5, PhC*H*$_2$CO), 5.39 (1H, br d, *J* = 7.4, CBzN*H*), 7.19 (2H, d, *J* = 6.9, ArH), 7.33–7.42 (8H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, $CDCl_3$) 33.2, 38.1, 59.0, 67.5, 127.6, 128.3, 128.5, 128.8, 129.2, 129.3, 135.6, 136.3, 155.7, 201.2.

4.2.5. (3-Bromo-1-(*S*)-(2-methylpropyl)-2-oxopropyl)carbamic acid benzyl ester 3e. Prepared from **2e** by the general method to give title compound **3e** as a pale yellow oil, yield 97%, $[\alpha]_D^{20} = -26.1$ (*c* 1, MeOH). Found: C 52.8; H 6.0; N 4.3, Br 23.5. $C_{15}H_{20}BrNO_3$ requires C 52; H 5.9; N 4.1, Br 23.4. ^{1}H NMR (δ/ppm, 500 MHz, $CDCl_3$) 0.92 + 0.94 (6H, 2 × d, *J* = 6.5, 2 × C*H*$_3$), 1.44 + 1.59 (2H, m, C*H*$_2$CH(CH$_3$)$_2$), 1.69 (1H, m, CH$_2$C*H* (CH$_3$)$_2$), 4.06 (2H, 2 × d, C*H*$_2$Br), 4.60 (1H, m, CBzNHC*H*), 5.07 (2H, 2 × d, PhC*H*$_2$CO), 5.52 (1H, br s, CBzN*H*), 7.27–7.37 (5H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, $CDCl_3$) 13.9, 21.5, 23.3, 24.9, 40.5, 56.6, 67.2, 128.1, 128.6, 128.8, 136.1, 156.3, 201.6.

4.2.6. (3-Bromo-1-(*S*)-(1-methylpropyl)-2-oxopropyl)carbamic acid benzyl ester 3f. Prepared from **2f** by the general method to give title compound **3f** as a white solid, yield 98%, mp 83–84 °C, $[\alpha]_D^{20} = -26.1$ (*c* 1, MeOH). Found: C 52.2; H 5.7; N 4.0, Br 23.0. $C_{15}H_{20}BrNO_3$ requires C 52.6; H 5.9; N 4.1, Br 23.4. ^{1}H NMR (δ/ppm, 500 MHz, $CDCl_3$) 0.87 (3H, t, $J = 7.3$, CH_2CH_3), 0.96 (3H, d, $J = 6.8$, $CHCH_3$), 1.07 + 1.31 (2H, 2 × m, CH_3CH_2), 1.92 (1H, m, $CH_3CHCH_2CH_3$), 4.04 (2H, 2 × d, $J = 13.7$, CH_2Br), 4.57 (1H, k, $J = 5.0$, CBzNHCH), 5.08 (2H, 2 × d, $PhCH_2CO$), 5.33 (1H, d, $J = 8.5$, CBzNH), 7.30–7.36 (5H, m, ArH). ^{13}C NMR (δ/ppm, 125 MHz, $CDCl_3$) 11.6, 16.2, 24.4, 33.3, 37.1, 62.8, 67.4, 128.3, 128.5, 128.8, 136.2, 156.5, 201.0.

4.2.7. 2-(*S*)-(2-Bromo-1-oxoethyl)pyrrolidine-1-carboxylic acid benzyl ester 3g. Prepared from **2g** by the general method to give title compound **3g** as a yellow oil, yield 95%, $[\alpha]_D^{20} = -5.1$ (*c* 1, MeOH). Found: C 51.2; H 5.0; N 4.1, Br 24.3. $C_{14}H_{16}BrNO_3$ requires C 51.6; H 4.9; N 4.3, Br 24.5. ^{1}H NMR (δ/ppm, 360 MHz, $CDCl_3$) 2.11 (2H, m, $CH_2CH_2CH_2$), 2.22 (2H, m, $CHCH_2CH_2$), 3.58 (2H, m, CH_2CH_2N), 4.42 (1H, m, CH_2CHN), 4.53 (2H, 2 × d, $J = 14.1$, CH_2Br), 5.18 (2H, 2 × d, $J = 12.4$, $PhCH_2CO$), 7.30–7.44 (5H, m, ArH). ^{13}C NMR (δ/ppm, 125 MHz, $CDCl_3$) 23.8 + 25.1, 29.6 + 31.0, 45.8 + 47.1, 52.5 + 53.0, 60.8, 67.5, 127.9, 128.1, 128.4, 128.6, 128.9, 136.1 + 136.6, 154.2 + 155.1, 194.8 + 195.7.

4.3. Condensation (general method)

A mixture of benzamidine hydrochloride (4.7 g, 30 mmol) and potassium bicarbonate (8.3 g, 60 mmol) in water (10 mL) and THF (40 mL) was stirred and heated to reflux. α-Bromoketone **3** (15 mmol) in THF (30 mL) was added into this refluxed mixture dropwise over a 1 h period. The reaction mixture was then heated at reflux overnight. THF was then removed under reduced pressure and water layer extracted with dichloromethane. The extract was washed with water and brine, dried and evaporated to afford crude product **4**, which was purified by silica gel chromatography (ethyl acetate–hexane 1:1).

4.3.1. 2-Phenyl-4-(1-(*S*)-benzyloxycarbonylaminoethyl)-1*H*-limidazole 4a. Prepared from **3a** by the general method to give title compound **4a** as a white solid, yield 89%, mp 152–153 °C, $[\alpha]_D^{20} = -25.4$ (*c* 1, MeOH). Found: C 70.9; H 6.0; N 13.2. $C_{19}H_{19}N_3O_2$ requires C 71.0; H 6.0; N 13.1. ^{1}H NMR (δ/ppm, 500 MHz, DMSO) 1.48 (3H, d, $J = 6.9$, CH_3), 4.78 + 4.90 (1H, m, CBzNHCH), 5.11 (2H, 2 × d, $PhCH_2CO$), 6.91 + 7.08 (1H, s, H_{im}), 7.35 + 7.49 (8H, m, ArH), 7.97 (2H, d, $J = 7.5$, ArH), 12.33 + 12.39 (1H, br s). ^{13}C NMR (δ/ppm, 125 MHz, DMSO) 21.3, 45.3, 65.1, 113.1, 124.8, 127.7, 127.8, 128.3, 128.7, 130.8, 137.4, 144.8, 144.9, 155.5. Positive-ion APCI-MS: *m*/*z* 322 $[M+H]^+$ (100%), 171 $[M+H-NH_2COOCH_2C_6H_5]^+$. Positive-ion APCI-MS/MS of *m*/*z* 322: 230 $[M+H-CH_3C_6H_5]^+$, 186 $[M+H-HCOOCH_2C_6H_5]^+$, 171 $[M+H-NH_2COOCH_2C_6H_5]^+$ (100%). Negative-ion APCI-MS: 320 $[M-H]^-$, 228 $[M-H-CH_3C_6H_5^-$, 212 $[M-H-HOCH_2C_6H_5]^-$, 186 $[M-COOCH_2C_6H_5]^-$, 169 $[M-H-NH_2COOCH_2C_6H_5]^-$ (100%). Negative-ion APCI-MS/MS of *m*/*z* 320: 275 $[M-H-NH_2COH]^-$, 212 $[M-H-HOCH_2C_6H_5]^-$, 210 $[M-H-CH_3C_6H_5-H_2O]^-$ (100%), 186 $[M-COOCH_2C_6H_5]^-$, 169 $[M-H-NH_2COOCH_2C_6H_5]^-$.

4.3.2. 2-Phenyl-4-(1-(*R*)-benzyloxycarbonylaminoethyl)-1*H*-limidazole 4b. Prepared from **3b** by the general method to give title compound **4b** as a white solid, yield 85%, mp 158–159 °C, $[\alpha]_D^{20} = +24.9$ (*c* 1, MeOH). Found: C 71.0; H 6.1; N 13.2. $C_{19}H_{19}N_3O_2$ requires C 71.0; H 6.0; N 13.1. ^{1}H NMR (δ/ppm, 500 MHz, DMSO) 1.48 (3H, d, $J = 6.9$, CH_3), 4.78 + 4.90 (1H, m, CBzNHCH), 5.11 (2H, 2 × d, $PhCH_2CO$), 6.91 + 7.08 (1H, s, H_{im}), 7.35 + 7.49 (8H, m, ArH), 7.97 (2H, d, $J = 7.5$, ArH), 12.33 + 12.39 (1H, br s). ^{13}C NMR (δ/ppm, 125 MHz, DMSO) 21.3, 45.3, 65.1, 113.1, 124.8, 127.7, 127.8, 128.3, 128.7, 130.8, 137.4, 144.8, 144.9, 155.5. Positive-ion APCI-MS: *m*/*z* 322 $[M+H]^+$ (100%), 171 $[M+H-NH_2COOCH_2C_6H_5]^+$. Positive-ion APCI-MS/MS of *m*/*z* 322: 230 $[M+H-CH_3C_6H_5]^+$, 186 $[M+H-HCOOCH_2C_6H_5]^+$, 171 $[M+H-NH_2COOCH_2C_6H_5]^+$ (100%). Negative-ion APCI-MS: 320 $[M-H]^-$, 228 $[M-H-CH_3C_6H_5]^-$, 212 $[M-H-HOCH_2C_6H_5]^-$, 186 $[M-COOCH_2C_6H_5]^-$, 169 $[M-H-NH_2COOCH_2C_6H_5]^-$ (100%). Negative-ion APCI-MS/MS of *m*/*z* 320: 275 $[M-H-NH_2COH]^-$, 212 $[M-H-HOCH_2C_6H_5]^-$, 210 $[M-H-CH_3C_6H_5-H_2O]^-$ (100%), 186 $[M-COOCH_2C_6H_5]^-$, 169 $[M-H-NH_2COOCH_2C_6H_5]^-$.

4.3.3. 2-Phenyl-4-(1-(*S*)-benzyloxycarbonylamino-2-methylpropyl)-1*H*-imidazole 4c. Prepared from **3c** by the general method to give the title compound **4c** as a white solid, yield 76%, mp 138–139 °C, $[\alpha]_D^{20} = -45.2$ (*c* 1, MeOH). Found: C 72.3; H 6.7; N 12.1. $C_{21}H_{23}N_3O_2$ requires C 72.2; H 6.6; N 12.0. ^{1}H NMR (δ/ppm, 500 MHz, DMSO) 0.89 (3H, d, $J = 6.7$, CH_3), 0.92 (3H, d, $J = 6.7$, CH_3), 2.06 + 2.15 (1H, m, $(CH_3)_2CH$), 4.50 + 4.60 (1H, m, CBzNHCH), 5.09 (2H, 2 × d $J = 17.2$, $PhCH_2CO$), 6.92 + 7.09 (1H, s, H_{im}), 7.34–7.49 (8H, m, ArH), 7.95 (2H, d, $J = 7.3$, ArH), 12.27 + 12.39 (1H, br s). ^{13}C NMR (δ/ppm, 125 MHz, DMSO) 18.4, 19.6, 32.2, 55.4, 65.2, 114.2, 124.6, 124.8, 127.7, 127.9, 128.4, 128.7, 130.8, 137.4, 143.0, 144.8, 156.1. Positive-ion APCI-MS: *m*/*z* 350 $[M+H]^+$ (100%), 306 $[M+H-propane]^+$, 240 $[M+H-CH_3C_6H_5-H_2O]^+$, 199 $[M+H-NH_2COOCH_2C_6H_5]^+$. Positive-ion APCI-MS/MS of *m*/*z* 350: 199 $[M+H-NH_2COOCH_2C_6H_5]^+$ (100%). Negative-ion APCI-MS: 348 $[M-H]^-$, 240 $[M-H-HOCH_2C_6H_5]^-$, 197 $[M-H-NH_2COOCH_2C_6H_5]^-$ (100%). Negative-ion APCI-MS/MS of *m*/*z* 348: 240 $[M-H-HOCH_2C_6H_5]^-$, 197 $[M-H-NH_2COOCH_2C_6H_5]^-$ (100%).

4.3.4. 2-Phenyl-4-(1-(*S*)-benzyloxycarbonylamino-2-phenylethyl)-1*H*-imidazole 4d. Prepared from **3d** by the general method to give title compound **4d** as a white solid, yield 65%, mp 171–172 °C, $[\alpha]_D^{20} = -13.5$ (*c* 1, $CHCl_3$). Found: C 75.7; H 5.9; N 10.6. $C_{25}H_{23}N_3O_2$ requires C 75.6; H 5.8; N 10.6. ^{1}H NMR (δ/ppm,

500 MHz, DMSO) 3.04 + 3.29 (2H, 2 × m, CH_2Ph), 4.91 (1H, k, J = 5.4, CBzNHCH), 5.02 (2H, 2 × d, PhCH_2CO), 6.95 + 7.08 (1H, s, H_{im}), 7.34–7.49 (8H, m, ArH), 7.94 (2H, d, J = 7.2, ArH), 12.43 (1H, br s,). ^{13}C NMR (δ/ppm, 125 MHz, DMSO) 40.8, 51.4, 65.0, 113.9, 124.9, 127.4, 127.5, 128.1, 128.3, 128.4, 128.8, 129.3, 131.3, 134.3, 137.5, 139.2, 143.7, 145.1, 155.7. Positive-ion APCI-MS: m/z 398 $[M+H]^+$ (100%), 306 $[M+H-CH_3C_6H_5]^+$, 262 $[M+H-HCOOCH_2C_6H_5]^+$, 247 $[M+H-NH_2COOCH_2C_6H_5]^+$. Positive-ion APCI-MS/MS of m/z 398: 247 $[M+H-NH_2COOCH_2C_6H_5]^+$ (100%). Negative-ion APCI-MS: 396 $[M-H]^-$, 262 $[M-COOCH_2C_6H_5]^-$, 245 $[M-H-NH_2COOCH_2C_6H_5]^-$ (100%). Negative-ion APCI-MS/MS of m/z 396: 245 $[M-H-NH_2COOCH_2C_6H_5]^-$ (100%).

4.3.5. 2-Phenyl-4-(1-(*S*)-benzyloxycarbonylamino-3-methylbutyl)-1*H*-imidazole 4e. Prepared from **3e** by the general method to give the title compound **4e** as a white solid, yield 88%, mp 146–147 °C, $[\alpha]_D^{20} = -48.7$ (c 1, MeOH). Found: C 72.6; H 7.0; N 11.7. $C_{22}H_{25}N_3O_2$ requires C 72.7; H 6.9; N 11.6. ^{1}H NMR (δ/ppm, 500 MHz, DMSO) 0.95 (6H, d, J = 5.6, CH(CH_3)$_2$), 1.69 (3H, m, CH_2CH), 4.71 + 4.82 (1H, m, CBzNHCH), 5.08 (2H, 2 × d, J = 15.9 Hz, PhCH_2CO), 6.87 + 7.04 (1H, s, H_{im}), 7.35–7.51 (8H, m, ArH), 7.94 (2H, d, J = 8.0, ArH), 12.28 + 12.35 (1H, br s). ^{13}C NMR (δ/ppm, 125 MHz, DMSO) 22.0, 23.0, 24.5, 44.3, 47.8, 65.1, 113.4, 124.8, 125.4, 127.7, 127.9, 128.4, 128.7, 130.8, 137.5, 144.6, 144.9, 155.8. Positive-ion APCI-MS: m/z 364 $[M+H]^+$ (100%), 228 $[M+H-HCOOCH_2C_6H_5]^+$, 213 $[M+H-NH_2COOCH_2C_6H_5]^+$ Positive-ion APCI-MS/MS of m/z 364: 272 $[M+H-CH_3C_6H_5]^+$, 228 $[M+H-HCOOCH_2C_6H_5]^+$, 213 $[M+H-NH_2COOCH_2C_6H_5]^+$ (100%), 157 $[M+H-NH_2COOCH_2C_6H_5-butene]^+$. Negative-ion APCI-MS: 362 $[M-H]^-$, 254 $[M-H-HOCH_2C_6H_5]^-$, 228 $[M-COOCH_2C_6H_5]^-$, 211 $[M-H-NH_2COOCH_2C_6H_5]^-$ (100%). Negative-ion APCI-MS/MS of m/z 362: 317 $[M-H-NH_2COH]^-$, 254 $[M-H-HOCH_2C_6H_5]^-$, 252 $[M-H-CH_3C_6H_5-H_2O]^-$, 211 $[M-H-NH_2COOCH_2C_6H_5]^-$ (100%).

4.3.6. 2-Phenyl-4-(1-(*S*)-benzyloxycarbonylamino-2-methylbutyl)-1*H*-imidazole 4f. Prepared from **3f** by the general method to give title compound **4f** as a white solid, yield 42%, mp 128–129 °C, $[\alpha]_D^{20} = -50.2$ (c 1, MeOH). Found: C 72.7; H 7.0; N 11.9. $C_{22}H_{25}N_3O_2$ requires C 72.7; H 6.9; N 11.6. ^{1}H NMR (δ/ppm, 500 MHz, DMSO) 0.83 (3H, d, J = 6.6, CHCH_3), 0.89 (3H, t, J = 7.3, CH$_2$CH_3), 1.14 + 1.53 (2H, m, CH$_3$CH_2), 1.82 + 1.90 (1H, m, CH$_3$CHCH$_2$CH$_3$), 4.55 + 4.66 (1H, t, J = 9.2, CBzNHCH), 5.07 (2H, J = 16.2, PhCH_2CO), 6.91 + 7.09 (1H, s, H_{im}), 7.35–7.7.48 (8H, m, ArH), 7.94 (2H, d, J = 7.6, ArH), 12.24 + 12.38 (1H, br s). ^{13}C NMR (δ/ppm, 125 MHz, DMSO) 11.4, 15.8, 24.8, 38.7, 54.2, 65.2, 114.3, 124.6, 124.8, 127.7, 127.9, 128.4, 128.7, 130.8, 137.4, 142.7, 144.7, 155.9. Positive-ion APCI-MS: m/z 364 $[M+H]^+$, 306 $[M+H-butane]^+$, 254 $[M+H-CH_3C_6H_5-H_2O]^+$, 213 $[M+H-NH_2COOCH_2C_6H_5]^+$ (100%). Positive-ion APCI-MS/MS of m/z 364: 213 $[M+H-NH_2COOCH_2C_6H_5]^+$ (100%), 171 $[M+H-NH_2COOCH_2C_6H_5-propene]^+$, 157 $[M+H-NH_2COOCH_2C_6H_5-butene]^+$. Negative-ion APCI-MS: 362 $[M-H]^-$, 254 $[M-H-HOCH_2C_6H_5]^-$, 211 $[M-H-NH_2COOCH_2C_6H_5]^-$ (100%). Negative-ion APCI-MS/MS of m/z 362: 211 $[M-H-NH_2COOCH_2C_6H_5]^-$ (100%).

4.3.7. 2-Phenyl-4-(1-benzyloxycarbonyl)pyrrolidine-2-(*S*)-yl-1*H*-imidazole 4g. Prepared from **3g** by the general method to give the title compound **4g** as a yellow oil, yield 70%, $[\alpha]_D^{20} = -34.2$ (c 1, MeOH). Found: C 72.3; H 5.9; N 12.1. $C_{21}H_{21}N_3O_2$ requires C 72.6; H 6.1; N 12.1. ^{1}H NMR (δ/ppm, 500 MHz, DMSO) 1.89 (2H, m, CH$_2$CH_2CH$_2$), 2.12 (2H, m, CHCH_2CH$_2$), 3.54 (2H, m, CH$_2$CH_2N), 4.98 (1H, m, CH$_2$CHN), 5.12 (2H, 2 × d, J = 13.0, PhCH_2CO), 6.98 (1H, s, H_{im}), 7.35–7.50 (8H, m, ArH), 7.94 (2H, d, J = 8.0, ArH), 12.38 + 12.40 (1H, br s). ^{13}C NMR (δ/ppm, 125 MHz, DMSO) 22.6 + 22.4, 31.8 + 32.9, 46.1 + 46.6, 55.3 + 55.7, 65.0 + 65.5, 113.7 + 113.9, 124.7, 127.5, 127.9, 128.3, 128.7, 130.8, 131.3, 134.3, 137.3, 145.0, 153.9 + 154.1. Positive-ion APCI-MS: m/z 348 $[M+H]^+$ (100%), 304 $[M+H-CO_2]^+$, 240 $[M+H-HOCH_2C_6H_5]^+$, 214 $[M-COOCH_2C_6H_5]^+$, 212 $[M+H-HCOOCH_2C_6H_5]^+$. Positive-ion APCI-MS/MS of m/z 348: 304 $[M+H-CO_2]^+$, 287 $[M+H-CO_2-NH_3]^+$ (100%), 240 $[M+H-HOCH_2C_6H_5]^+$, 212 $[M+H-HCOOCH_2C_6H_5]^+$, 197 $[M+H-HOCH_2C_6H_5-NHCO]^+$, 145 $[C_6H_5(C{=}NCH{=}CHNH_2)]^+$. Negative-ion APCI-MS: 346 $[M-H]^-$ (100%), 238 $[M-H-HOCH_2C_6H_5]^-$. Negative-ion APCI-MS/MS of m/z 346: 238 $[M-H-HOCH_2C_6H_5]^-$ (100%), 210 $[M-H-HOCH_2C_6H_5-CO]^-$, 195 $[M-H-HOCH_2C_6H_5-CO-CH_3]^-$.

4.4. Deprotection (general method)

The Pd catalyst on active carbon (0.5 g, 10%, Aldrich) was added into the protected imidazole **4** (15 mmol) solution in methanol (80 mL) and the reaction mixture in pressure vessel saturated with hydrogen (300 kPa) until TLC showed reaction completion. Filtration and evaporation of the solvent gave the pure product **5**.

4.4.1. 2-Phenyl-4-(1-(*S*)-aminoethyl)-1*H*-limidazole 5a. Prepared from **4a** by the general method to give title compound **5a** as a white solid, yield 99%, mp 158–160 °C, $[\alpha]_D^{20} = +4.1$ (c 1, MeOH). Found: C 70.6; H 7.0; N 22.3. $C_{11}H_{13}N_3$ requires C 70.6; H 7.0; N 22.4.1. ^{1}H NMR (δ/ppm, 500 MHz, DMSO) 1.55 (3H, d, J = 6.8, CH_3), 4.37 (1H, k, J = 6.7, NH$_2$CH), 7.22 (1H, s, H_{im}), 7.37 (1H, t, J = 7.2, ArH), 7.48 (2H, t, J = 7.6, ArH), 8.03 (2H, d, J = 7.3, ArH). ^{13}C NMR (δ/ppm, 125 MHz, DMSO) 19.6, 43.9, 118.5, 124.1, 124.9, 128.1, 128.7, 130.7, 145.8. Positive-ion APCI-MS: m/z 188 $[M+H]^+$, 171 $[M+H-NH_3]^+$ (100%). Positive-ion APCI-MS/MS of m/z 188: 171 $[M+H-NH_3]^+$ (100%). Negative-ion APCI-MS: 186 $[M-H]^-$, 169 $[M-H-NH_3]^-$ (100%). Negative-ion APCI-MS/MS of m/z 186: 169 $[M-H-NH_3]^-$ (100%), 143 $[C_6H_5(C{=}NCH{=}CNH)]^-$.

4.4.2. 2-Phenyl-4-(1-(*R*)-aminoethyl)-1*H*-limidazole 5b Prepared from **4b** by the general method to give the title compound **5b** as an oil, yield 99%, $[\alpha]_D^{20} = -4.0$ (c

1, MeOH). Found: C 70.3; H 6.9; N 22.1. $C_{11}H_{13}N_3$ requires C 70.6; H 7.0; N 22.4.1. ^{1}H NMR (δ/ppm, 500 MHz, DMSO) 1.55 (3H, d, J = 6.8, CH_3), 4.37 (1H, k, J = 6.7, NH_2CH), 7.22 (1H, s, H_{im}), 7.37 (1H, t, J = 7.2, ArH), 7.48 (2H, t, J = 7.6, ArH), 8.03 (2H, d, J = 7.3, ArH). ^{13}C NMR (δ/ppm, 125 MHz, DMSO) 19.6, 43.9, 118.5, 124.1, 124.9, 128.1, 128.7, 130.7, 145.8. Positive-ion APCI-MS: m/z 188 $[M+H]^+$, 171 $[M+H-NH_3]^+$ (100%). Positive-ion APCI-MS/MS of m/z 188: 171 $[M+H-NH_3]^+$ (100%). Negative-ion APCI-MS: 186 $[M-H]^-$, 169 $[M-H-NH_3]^-$ (100%). Negative-ion APCI-MS/MS of m/z 186: 169 $[M-H-NH_3]^-$ (100%), 143 $[C_6H_5(C{=}NCH{=}CNH)]^-$.

4.4.3. 2-Phenyl-4-(1-(*S*)-amino-2-methylpropyl)-1*H*-imidazole 5c. Prepared from **4c** by the general method to give the title compound **5c** as an oil, yield 99%, $[\alpha]_D^{20} = +2.7$ (c 1, MeOH). Found: C 72.1; H 7.9; N 19.5. $C_{13}H_{17}N_3$ requires C 72.5; H 8.0; N 19.5. ^{1}H NMR (δ/ppm, 500 MHz, DMSO) 0.89 (3H, d, J = 5.7, CH_3), 0.90 (3H, d, J = 5.7, CH_3), 1.98 (1H, m, $(CH_3)_2CH$), 3.66 (1H, d, J = 5.7, NH_2CH), 6.96 (1H, s, H_{im}), 7.34 (1H, t, J = 7.4, ArH), 7.45 (2H, t, J = 7.8, ArH), 7.95 (2H, d, J = 7.4, ArH). ^{13}C NMR (δ/ppm, 125 MHz, DMSO) 18.1, 19.6, 33.6, 48.7, 117.3, 124.5, 124.7, 126.7, 128.7, 131.1, 144.6. Positive-ion APCI-MS: m/z 216 $[M+H]^+$, 199 $[M+H!-NH_3]^+$ (100%). Positive-ion APCI-MS/MS of m/z 216: 199 $[M+H-NH_3]^+$ (100%). Negative-ion APCI-MS: 214 $[M-H]^-$, 197 $[M-H-NH_3]^-$ (100%). Negative-ion APCI-MS/MS of m/z 214: 197 $[M-H-NH_3]^-$ (100%).

4.4.4. 2-Phenyl-4-(1-(*S*)-amino-2-phenylethyl)-1*H*-imidazole 5d. Prepared from **4d** by the general method to give title compound **5d** as a white solid, mp 80–81 °C, yield 99%, $[\alpha]_D^{20} = +23.9$ (c 1, MeOH). Found: C 77.3; H 6.5; N 15.9. $C_{17}H_{17}N_3$ requires C 77.5; H 6.5; N 16.0. ^{1}H NMR (δ/ppm, 500 MHz, DMSO) 2.97 + 3.20 (2H, 2 × m, CH_2Ph), 4.21 (1H, t, J = 7.0, NH_2CH), 6.99 (1H, s, H_{im}), 7.19–7.30 (4H, m, ArH), 7.37 (1H, t, J = 7.3, ArH), 7.47 (2H, t, J = 7.5, ArH), 7.99 (2H, d, J = 7.3, ArH). ^{13}C NMR (δ/ppm, 125 MHz, DMSO) 43.9, 50.7, 118.0, 124.9, 125.4, 126.1, 128.0, 128.2, 128.8, 129.4, 131.0, 139.7, 145.0. Positive-ion APCI-MS: m/z 264 $[M+H]^+$, 247 $[M+H-NH_3]^+$ (100%), 143 $[C_6H_5(C{=}NCH{=}CNH)]^+$. Positive-ion APCI-MS/MS of m/z 264: 247 $[M+H-NH_3]^+$ (100%). Negative-ion APCI-MS: 262 $[M-H]^-$, 245 $[M-H-NH_3]^-$ (100%). Negative-ion APCI-MS/MS of m/z 262: 245 $[M-H-NH_3]^-$, 170 $[M-H-CH_3C_6H_5]^-$ (100%), 143 $[C_6H_5(C{=}NCH{=}CNH)]^-$.

4.4.5. 2-Phenyl-4-(1-(*S*)-amino-3-methylbutyl)-1*H*-imidazole 5e. Prepared from **4e** by the general method to give title compound **5e** as an oil, yield 99%, $[\alpha]_D^{20} = +2.6$ (c 1, MeOH). Found: C 73.2; H 8.2; N 18.1. $C_{14}H_{19}N_3$ requires C 73.3; H 8.4; N 18.3. ^{1}H NMR (δ/ppm, 500 MHz, DMSO) 0.91 (3H, d, J = 6.1, $CH(CH_3)_2$), 0.94 (3H, d, J = 6.2, $CH(CH_3)_2$) 1.55 (1H, m, CH_2CH), 1.67 (2H, m, $CHCH_2$) 3.95 (1H, m, NH_2CH), 7.02 (1H, s, H_{im}), 7.35 (1H, t, J = 7.3, ArH), 7.46 (2H, t, J = 7.4, ArH), 7.97 (2H, d, J = 7.3, ArH). ^{13}C NMR (δ/ppm, 125 MHz, DMSO) 22.3, 22.8, 24.4, 46.0, 46.7, 118.1, 124.8, 125.1, 127.8, 128.7, 130.5, 145.1. Positive-ion APCI-MS: m/z 230 $[M+H]^+$, 213 $[M+H-NH_3]^+$ (100%). Positive-ion APCI-MS/MS of m/z 230: 213 $[M+H-NH_3]^+$ (100%), 172 [M+H-butane]$^+$. Negative-ion APCI-MS: 228 $[M-H]^-$, 211 $[M-H-NH_3]^-$ (100%). Negative-ion APCI-MS/MS of m/z 228: 211 $[M-H-NH_3]^-$ (100%), 196 $[M-H-NH_3-CH_3]^-$, 184 $[M-H-NH_3-HCN]^-$, 169 $[M-H-NH_3-\text{propene}]^-$, 143 $[C_6H_5(C{=}NCH{=}CNH)]^-$.

4.4.6. 2-Phenyl-4-(1-(*S*)-amino-2-methylbutyl)-1*H*-imidazole 5f. Prepared from **4f** by the general method to give title compound **5f** as an oil, yield 99%, $[\alpha]_D^{20} = +4.5$ (c 1, MeOH). Found: C 73.4; H 8.4; N 18.5. $C_{14}H_{19}N_3$ requires C 73.3; H 8.4; N 18.3. ^{1}H NMR (δ/ppm, 360 MHz, DMSO) 0.85–0.92 (6H, m, $CHCH_3$ + CH_2CH_3), 1.13+1.54 (2H, 2 × m, CH_3CH_2), 1.84 (1H, m, $CH_3CHCH_2CH_3$), 3.88 (1H, m, NH_2CH), 7.07 (1H, s, H_{im}), 7.35 (1H, t, J = 7.2, ArH), 7.46 (2H, t, J = 7.7, ArH), 7.97 (2H, d, J = 7.3, ArH). ^{13}C NMR (δ/ppm, 125 MHz, DMSO) 11.6, 15.4, 24.9, 38.8, 53.3, 117.9, 124.9, 125.1, 128.0, 128.8, 130.8, 145.1. Positive-ion APCI-MS: m/z 230 $[M+H]^+$, 213 $[M+H-NH_3]^+$ (100%), 172 [M+H−butane]$^+$. Positive-ion APCI-MS/MS of m/z 230: 213 $[M+H-NH_3]^+$ (100%). Negative-ion APCI-MS: 228 $[M-H]^-$, 211 $[M-H-NH_3]^-$ (100%). Negative-ion APCI-MS/MS of m/z 228: 211 $[M-H-NH_3]^-$ (100%), 196 $[M-H-NH_3$-$CH_3]^-$, 184 $[M-H-NH_3-HCN]^-$, 169 $[M-H-NH_3-\text{propene}]^-$, 143 $[C_6H_5(C{=}NCH{=}CNH)]^-$.

4.4.7. 2-Phenyl-4-pyrrolidine-2-(*S*)-yl-1*H*-imidazole 5g. Prepared from **4g** by the general method to give the title compound **5g** as a yellow oil, yield 99%, $[\alpha]_D^{20} = +12.1$ (c 1, MeOH). Found: C 73.0; H 7.0; N 19.4. $C_{13}H_{15}N_3$ requires C 73.2; H 7.1; N 19.7. ^{1}H NMR (δ/ppm, 360 MHz, DMSO) 1.77 (3H, m, $CH_2CH_2CH_2$ + $CHCH_2CH_2$), 2.05 (1H, m, $CHCH_2CH_2$) 2.83 (1H, m, CH_2CH_2NH), 3.03 (1H, m, CH_2CH_2NH), 4.08 (1H, m, CH_2CHNH), 7.03 (1H, s, H_{im}), 7.35 (1H, t, J = 7.1, ArH), 7.46 (2H, t, J = 7.8, ArH), 7.95 (2H, d, J = 7.4, ArH). ^{13}C NMR (δ/ppm, 90 MHz, DMSO) 25.1, 33.2, 46.1, 54.2, 118.7, 124.7, 125.2, 127.8, 128.7, 131.0, 144.9. Positive-ion APCI-MS: m/z 214 $[M+H]^+$, 197 $[M+H-NH_3]^+$ (100%). Positive-ion APCI-MS/MS of m/z 214: 197 $[M+H-NH_3]^+$ (100%), 171 $[M+H-NH_3-C_2H_4]^+$. Negative-ion APCI-MS: 212 $[M-H]^-$ (100%). Negative-ion APCI-MS/MS of m/z 212: 195 $[M-H-NH_3]^-$ (100%).

Acknowledgements

Support of this research under Grant 203/02/0750 from the Czech Grant Agency is gratefully acknowledged. Authors would like to thanks to M. Holčapek for precise MS spectra recording (grant project No. 203/05/2106 sponsored by the Grant Agency of the Czech Republic).

References

1. Tao, Ye.; McKervey, M. A. *Tetrahedron* **1992**, *48*(37), 8007–8022.
2. Groarke, M.; McKervey, M. A.; Nieuwenhuyzen, M. *Tetrahedron Lett.* **2000**, *41*, 1275–1278.
3. Darkins, P.; Groarke, M.; McKervey, M. A.; Moncrieff, H. M.; McCarthy, N.; Nieuwenhuyzen, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 381–389.
4. Balenovic, K.; Cerar, D.; Filipovic, L. *J. Org. Chem.* **1953**, *18*, 868–871.
5. Balenovic, K.; Bregant, N. *J. Org. Chem.* **1952**, *17*, 1328–1330.
6. Borkovec, J.; Michalsky, J.; Rabusic, E.; Hadacek, J. *Chem. Pap.* **1954**, *48*, 717–721.
7. Li, B.; Chiu, C. K.-F.; Hank, R. F.; Murry, J.; Roth, J.; Tobiassen, H. *Org. Process Res. Dev.* **2002**, *6*(5), 682–683.