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A base promoted multigram synthesis of aminoisoxazoles: valuable building blocks for drug discovery and peptidomimetics†

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A practical multigram metal free synthesis of isoxazole-containing building blocks from commercially available amino acids was elaborated. The key reaction was a regioselective [3 + 2]-cycloaddition of *in situ* generated nitrile oxides with alkynes/enamines. The obtained building blocks were used in the preparation of bioactive compounds and peptidomimetics.

Introduction

The isoxazole core is a structural element in many commercial pharmaceuticals (Fig. 1). The range of biological activities of the isoxazole-containing drugs is broad: analgesic,[1] anti-inflammatory,[1a,c,2] anthelmintic,[3] anti-depressant,[4] anti-bacterial,[5] anticancer,[6] insecticidal,[7] nootropic,[8] anxiolytic,[8a] neuroprotective,[9] and HIV-inhibitory agents.[10] In this context, the development of practical methods towards isoxazole-based building blocks from common cheap starting materials is truly desirable.

Nitrile oxides are useful intermediates towards the synthesis of a wide plethora of isoxazole-based architectures.[11a–h] However; most of these methods either utilize toxic metals or hypervalent iodine compounds[11h] which in turn, are not environmentally friendly. At the same time, there are just a few known reports dealing with metal-free conditions and most common are based on the use of triethylamine[12a–b] and sodium perchlorate/triethylamine.[12c] Therefore, the development of metal-free protocols towards the synthesis of compounds bearing isoxazole core is of particular interest.[12d,e]

The use of amino acids[13a–h] in construction of isoxazole-containing compounds has been known before. However, these reports, dealt with the specific amino acids, and the studies have not been performed systematically on large variety of substrates. Taking into account the need of exploration of metal-free protocols as well as search for easily available substrates, herein we would like to elaborate on a general practical multigram metal-free synthesis of isoxazole-core building blocks starting from commonly available and diverse α-, β- and γ-amino acids.

Results and discussion

Synthesis

1. Synthesis of chloroximes from amino acids. The initial synthesis step was reduction of the amino acid carboxyl-groups in a number of N-Boc protected amino acids. Resulting N-Boc amino alcohols were subsequently oxidized into the corresponding aldehydes (Table 1). These aldehydes formed oximes upon treatment with hydroxylamine under mildly basic conditions (sodium hydrogen carbonate). The oximes were then treated with *N*-chlorosuccinimide under acidic conditions to afford the target N-Boc protected chloroximes **1–7** in good yields. The products were white powders that could be stored at room temperature for at least several months as exemplified in Table 1.

2. Synthesis of N-Boc aminoisoxazoles *via* [3 + 2]-cycloaddition. It is worth mentioning that our methodology for the synthesis of variety isoxazoles is known and here we would just mention some selected examples where the similar conditions like base or reaction temperatures were applied. Johnson *et al.* reported on the regioselective synthesis of 3,4-disubstituted isoxazoles between enolsilanes and nitrile

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† Electronic supplementary information (ESI) available: Experimental procedure and characterization of all new compounds (PDF). CCDC [1442715 and 1442716]. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ra02365g

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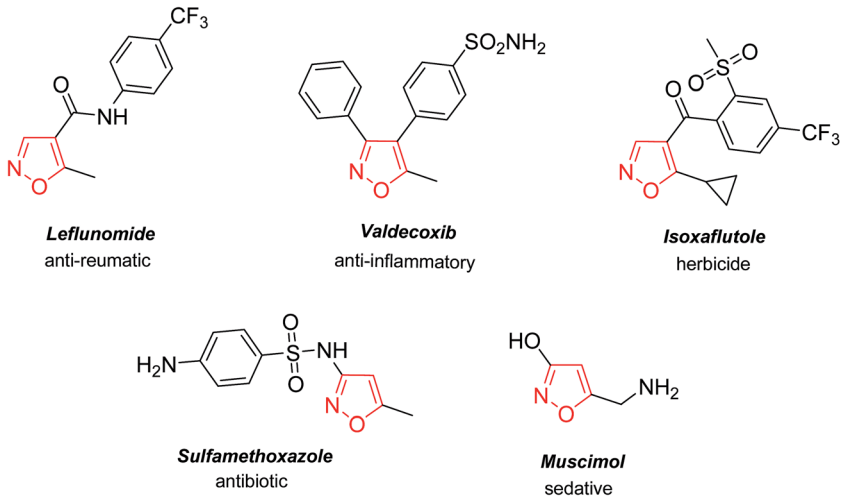

Fig. 1 Commercialized biologically active derivatives of isoxazole.

oxides.[14] In the same vein, the Zhu group and later Wang and co-workers reported on the synthesis of 3,4-disubstituted isoxazoles in high yields.[15a,b] The key point of the reported protocols was the reaction of *in situ* generated enamines from corresponding ketones or β-keto esters and nitrile oxides. Caddick and co-workers reported and interesting strategy towards the synthesis of 3,5-disubstituted isoxazoles bearing sulfonamide group at the 5-position.[16] Later the Shibata group developed the strategy for the synthesis of isoxazole triflones.[17] Hamme *et al.* reported on the synthesis of 3,5-disubstituted isoxazoles with electron withdrawing group at the 5-position by the reaction of 1,1-disubstituted bromoalkenes with nitrile oxides.[18a,b] Last but not least Schmidt and co-workers reported on the regioselective synthesis of 4-trifluorosubstituted isoxazoles in good yields.[19] All the aforementioned methods avoided the usage of metal-mediated reactions which prompted us to follow the similar conditions in order to synthesize a large panel of aminoisoxazoles in large scale.

In our case, synthesis of isoxazoles from the corresponding *in situ* generated nitrile oxides and alkynes/enamines was analogous to the mentioned above methods. Namely, treatment of chloroximes **1–7** with a mild base (sodium hydrogen carbonate or triethylamine) at either the room temperature or at 0 °C led to generation of corresponding nitrile oxides (Table 2). Subsequent addition of enamines **8–10** (1.2 eq.) to these *in situ* generated nitrile oxides lead to [3 + 2]-cycloaddition intermediates that readily eliminated dimethylamine to give the 3,4-disubstituted isoxazoles in a regioselective fashion as previously reported with push–pull enamines (Table 2, A).[20] In contrast, terminal alkynes **11**, **12** afforded a mixture of 3,4-/3,5-isomers ∼30/70 when reaction was performed at the room temperature.[21] Nevertheless, the same reaction at 0 °C exhibited an improved regioselectivity of ∼10/90, and the major 3,5-disubstituted isomers were easily isolated by column chromatography.[22]

While the above described [3 + 2] cycloaddition reactions were performed in ethyl acetate the synthesis also worked well in tetrahydrofuran, dichloromethane, dimethoxymethane or chloroform, though with compromised regioselectivity. At the same time synthesis of isoxazoles in water as environmentally benign solvent is of high interest.[23] It is also worth mentioning, that these reactions were performed under obligatory high dilution – substrate/solvent = 1/10 (wt/v) – otherwise formation of side furoxans was observed.[24]

As the result we obtained a variety of N-Boc aminoisoxazoles initially starting from amino acids, and the synthetic approach was scalable such that up to 50 g of a product (Boc-**6**-H) was obtained in a single synthesis run.

3. Synthesis of isoxazole-containing amines and amino acids. We also made several forays toward the cleavage of TMS-group utilizing K_2CO_3 or trifluoroacetic acid (TFA) as TMS-scavengers,[25] but unfortunately in our case the described procedure was not that efficient, furnishing the desired products in moderate yields. Moreover, attempts to cleave TMS-group with 4 M HCl in dioxane were also not optimal giving low yields. Though, these forays were not successful, it allowed us to improve our tactics. As a result, we found that cleavage of the TMS-group from the isoxazole core was easily achieved by treatment with catalytic amounts of KHF_2 in methanol–water mixture. Resulting 3-substituted isoxazoles were obtained in excellent yields (Table 3).

As next, cleavage of N-Boc group from all compounds was performed under acidic conditions to afford the target building blocks – aminoisoxazoles (Table 4).

Carboxymethyl-substituted isoxazoles were saponificated with sodium hydroxide in methanol to afford corresponding free amino acids in good yields (Table 5).

The structures of two final compounds were confirmed by X-ray analysis (Fig. 2). Interestingly, the structure of Boc-**4A**-COMe indicates a repulsion occurring between the carbamate carbonyl oxygen and the isoxazole nitrogen, similar to what has been recently reported for analogous structures with 1,3-oxa/thiazine in place of the isoxasole.[26]

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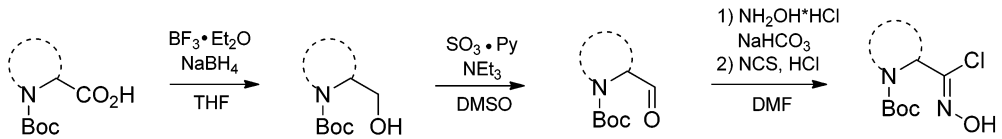
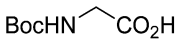
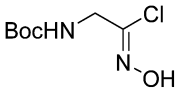
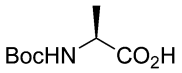
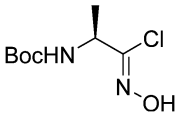
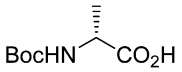
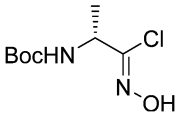
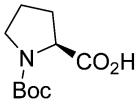
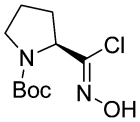
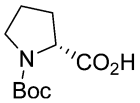
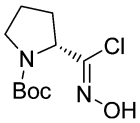
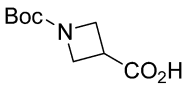
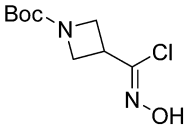
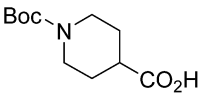
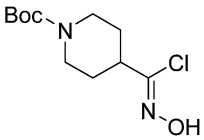
Table 1 Chloroximes synthesized starting from N-Boc amino acids



Boc-amino acid		Chloroxime		Yield[a]	Storage[b]
Boc-Gly		1		49%	>2 years
Boc-(*S*)-Ala		2		68%	≤0.5 years[c]
Boc-(*R*)-Ala		3		67%	≤0.5 years[c]
Boc-(*S*)-Pro		4		70%	>2 years
Boc-(*R*)-Pro		5		71%	>2 years
Boc-Aze		6		65%	>2 years
Boc-Pip		7		73%	>2 years

[a] Overall yield over four steps. [b] The products were stored in closed flasks at the room temperature. [c] The products were stored at 0 °C under argon. After six months *ca.* 10% decomposition was found according to ^{1}H NMR.

Practical applications

After having established a practical general synthetic protocol towards isoxazole-containing building blocks, we also aimed to demonstrate applicability of the synthesized structures in other chemical areas.

1. Synthesis of a drug candidate. **ABT-418** is a known nootropic agent.[27a] Recently, chemists at Abbott Laboratories synthesized its bioisostere **16** in four steps and 7.3% total yield starting from **4** and 2-bromopropene.[27b] Herein, we have developed an alternative approach to afford compound **16** (Scheme 1). First, [3 + 2]-cycloaddition between allylbromide and nitrile oxide generated from chloroxine **4** gave isoxazoline **13** in 95% yield. Next, elimination of hydrogen bromide under basic conditions gave isoxazole **14**. Cleavage of the N-Boc group produced free amine **15**, which was then subjected to reductive amination with aqueous formaldehyde to afford the target product **16** in gram quantities. The overall yield of the synthesis was 55% over 5 steps.

2. Synthesis of peptidomimetics. We also envisioned that chiral aminoisoxazoles could be used to prepare conformationally restricted peptidomimetics.[28] In this case the heterocyclic fragment will act as a rigid peptide bond substitute[29] (Scheme 2).

In addition, isomeric oxazoles and thiazoles are common in the backbones[30] of various ribosomally synthesized and post-translationally modified peptides.[31] Construction of an azole

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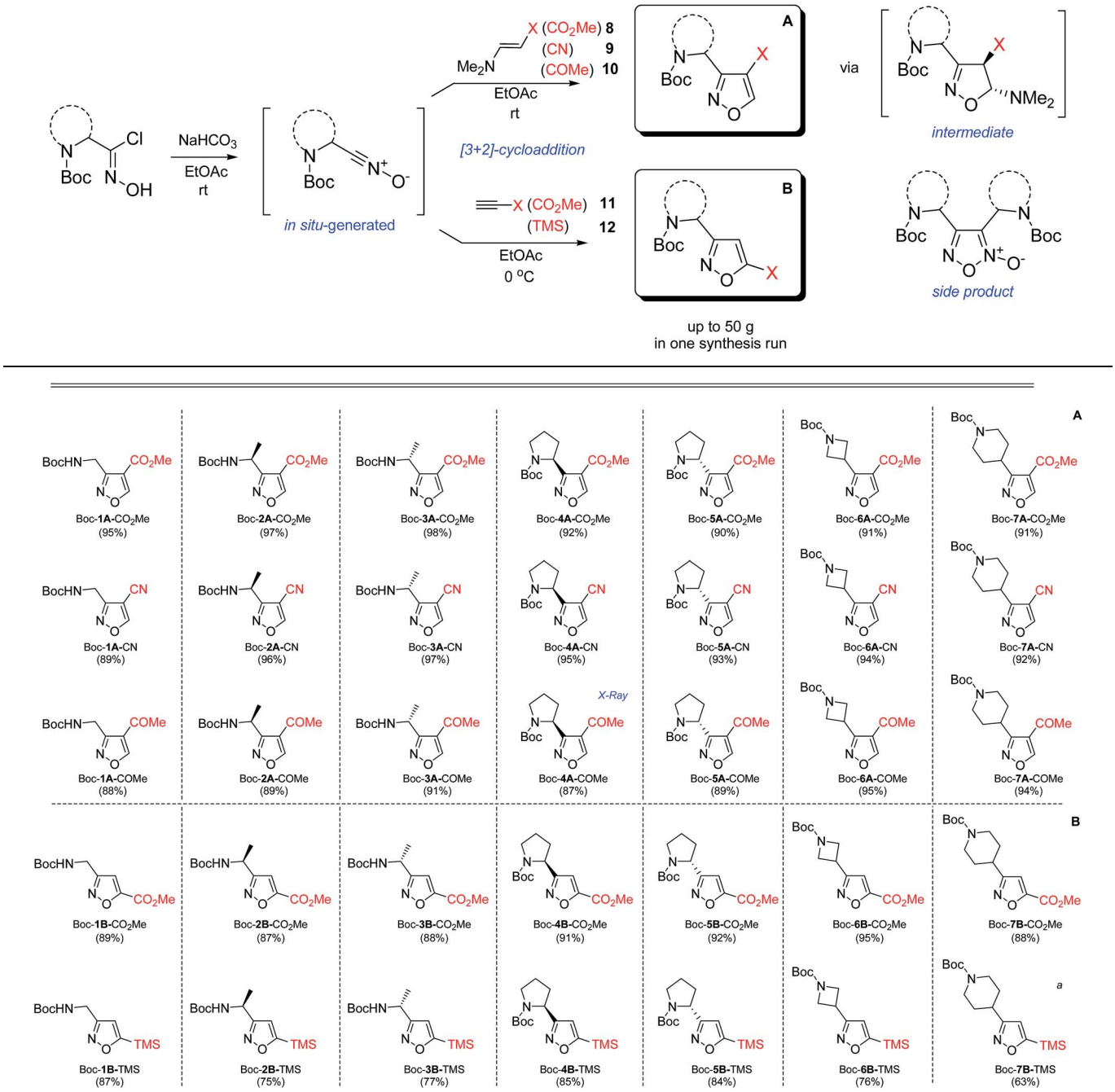
Table 2 The synthesis of N-Boc aminoisoxazoles *via* [3 + 2]-cycloaddition



[a] Et_3N was used instead of $NaHCO_3$ to generate the nitrile oxide, 5 eq. of **12** were used.

ring is generally afforded in nature by cyclization of serine or threonine side chain on the downstream amide bond.[32–34] Total synthesis of respective peptidomimetics has been developed in order to provide naturally occurring antimicrobial agents or toxins as well as their chemically modified analogues.[35,36] Though, oxa/thiazole to isoxazole mutations have not been explored. Therefore, next we attempted the synthesis of isoxazole-containing peptidomimetics by solid phase peptide synthesis (SPPS) in order to highlight this opportunity.

Initially we synthesized the Fmoc-protected amino acid Fmoc-AlaIso-OH (**17**) (Scheme 3). Peptide chains were grown on Rink-amide resin, and TBTU/HOBt/DIPEA system was used for coupling. Only in the case of Ac-Leu-AlaIso-Val-NH_2 (**18**) we observed minor degree of epimerization (≤15%), whereas in Ac-

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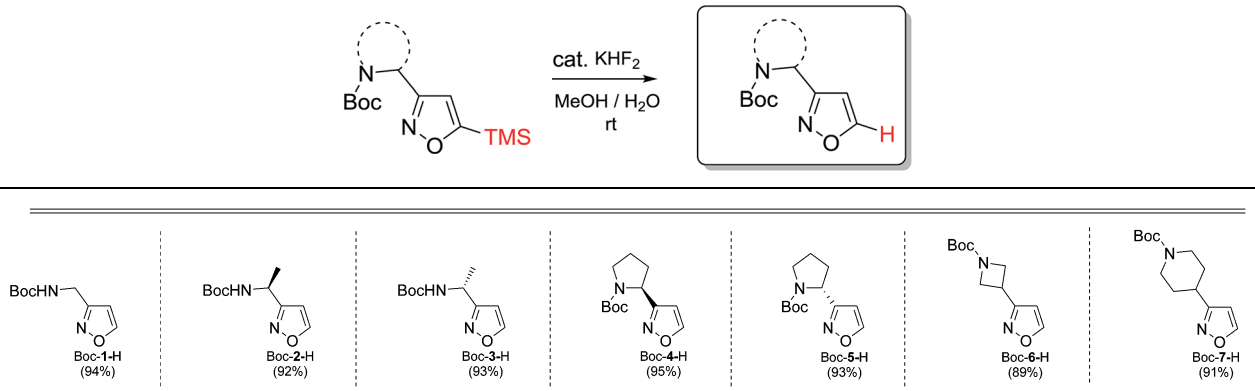
Table 3 Cleavage of TMS-group from the isoxazole ring



Leu-Val-AlaIso-NH_2 (**19**) no racemization was observed.[37] In addition, no degradation was found after cleavage from the resin upon treatment with TFA/TIS. Generally the amino acid Fmoc-AlaIso-OH turned out to be compatible with the standard SPPS, allowing synthesis and isolation of both target peptides by conventional methods.[38]

Table 4 Cleavage of the N-Boc protection group from the amino moiety

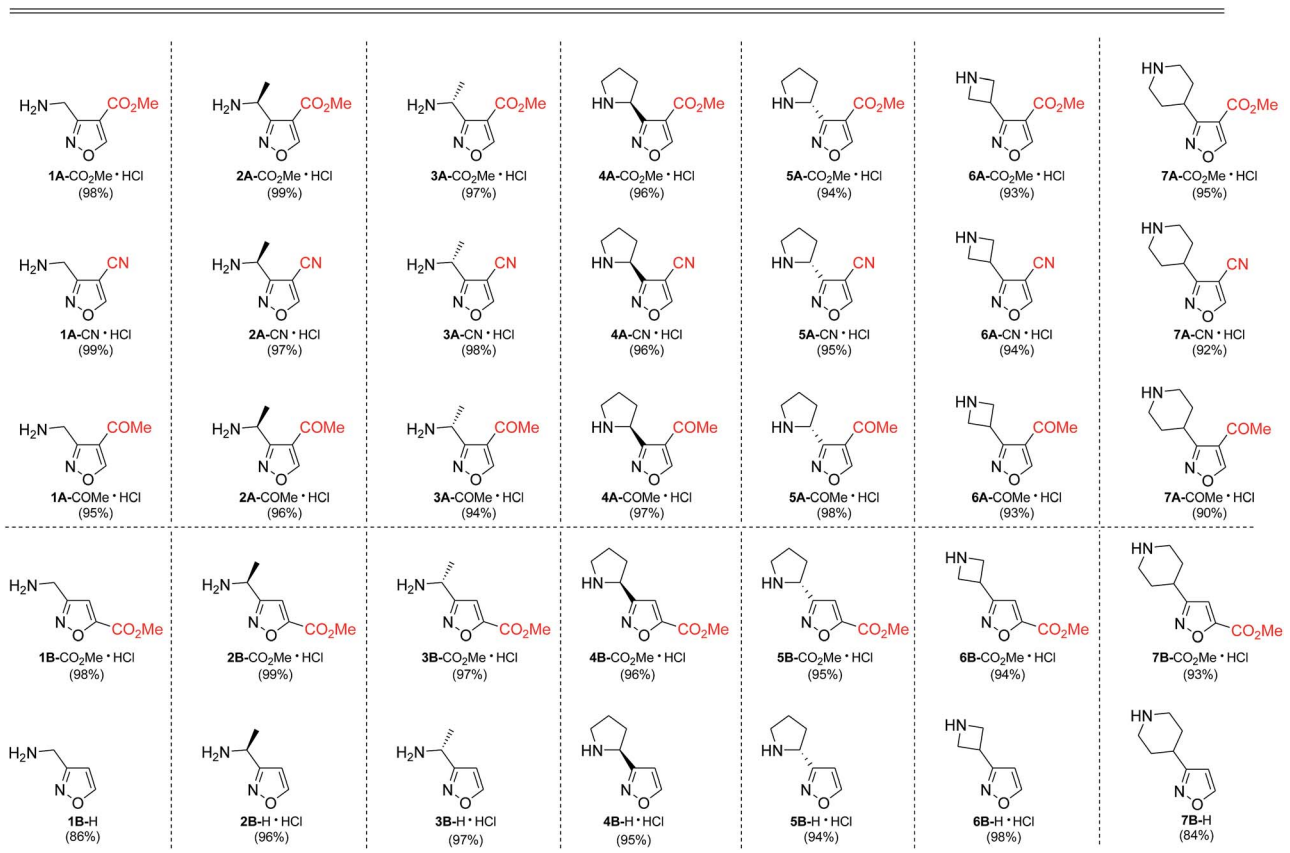


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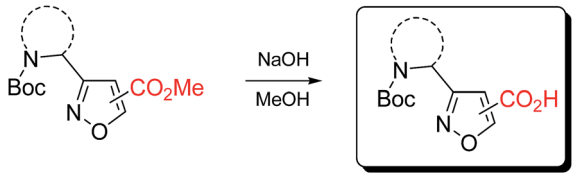
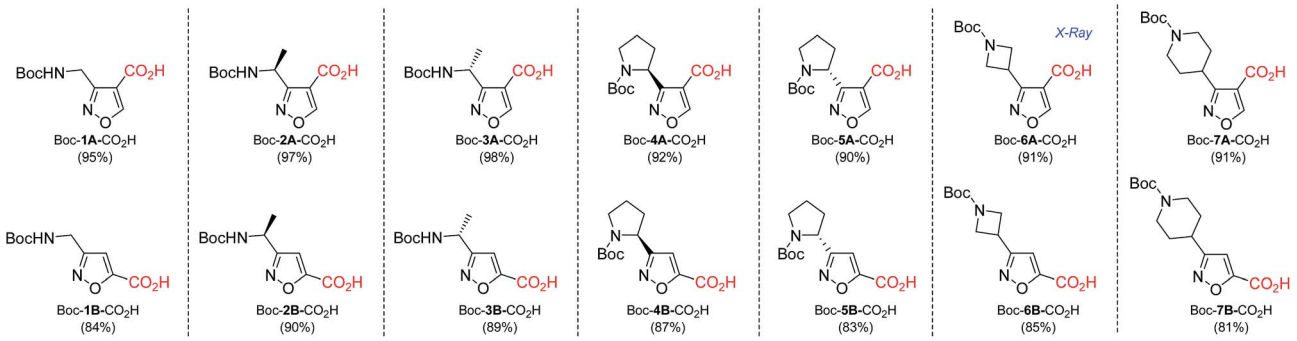
Table 5 Synthesis of isoxazole-containing amino acids





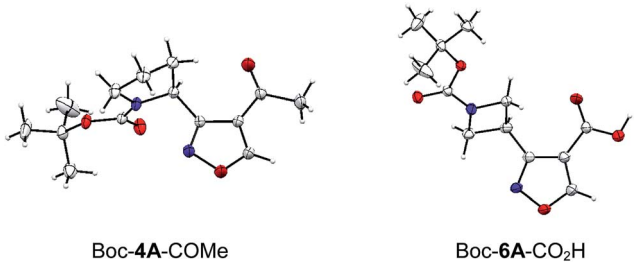


Fig. 2 X-ray crystal structures of Boc-**4A**-COMe and Boc-**6A**-CO_2H.

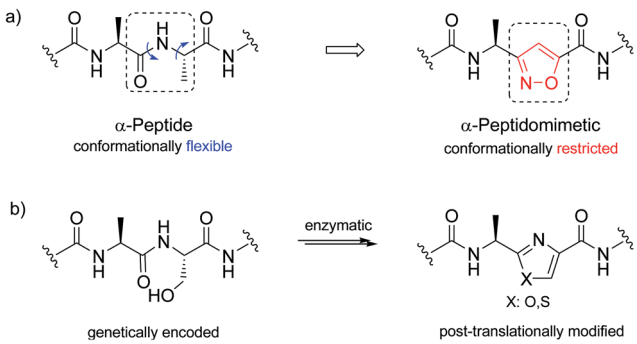
Conclusions

We have developed a general metal-free practical protocol towards isoxazole-containing building blocks starting from commonly available α-, β- and γ-amino acids. The target products were obtained in up to 50 g scale. The high potential of the developed method was demonstrated by synthesis of compound **16** – bioisostere of the known nootropic agent **ABT-418**, – and preparation of isoxazole-containing peptidomimetics **18, 19** by solid phase peptide synthesis.

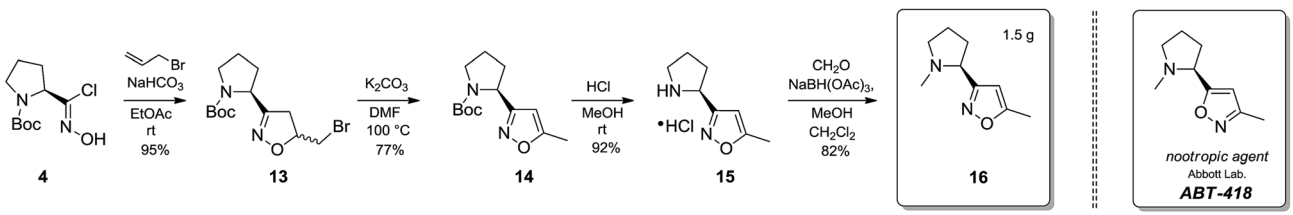
Experimental section

General

All reagents were available from Enamine Ltd. Solvents were purified according to standard procedures. When organic solutions were concentrated under reduced pressure, 35–40 °C bath temperature was used. Column chromatography was performed



Scheme 2 (a) α-Peptide, and its conformationally-restricted analogue with isoxazole backbone; (b) construction of a post-translationally modified peptide with oxa/thiasole backbone.



Scheme 1 Synthesis of isoxazole **16** – bioisostere of the known nootropic agent **ABT-418**.

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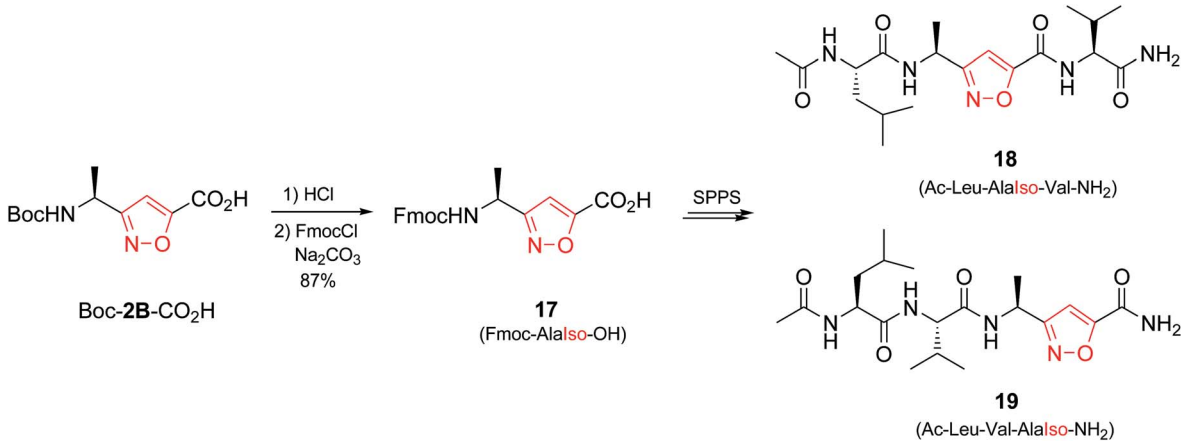

Scheme 3 Synthesis of isoxazole-containing peptidomimetics **18** and **19**.

with silica gel 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C NMR spectra were recorded at the NMR spectrometers operating at 400 and 500 ^{1}H frequency (101 and 126 MHz for ^{13}C experiments). NMR chemical shifts are reported in ppm, in the δ scale and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6, and 4.79 ppm for ^{1}H in D_2O. For peptides NMR analysis was performed in 5 mM peptide solutions in CD_3OD at 700 MHz (^{1}H frequency) spectrometer. ^{1}H NMR spectra were recorded 25 min after the peptides were dissolved (fresh) and therefore contained few of the non-exchanged amide resonances. The ^{1}H NMR spectra were in addition recorded after overnight measurements when the NH-to-ND exchange was already completed. ^{1}H HOHAHA (dipsi2 of 60 ms) and ROESY (spin-lock 300 ms) spectra were recorded to complete the assignment of the ^{1}H resonances. ^{13}C {^{1}H} dept45 and ^{1}H {^{13}C} HSQC experiments were performed in order to assign accompanied ^{13}C resonances. The following abbreviations are used in reported NMR data: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), br (broad), brs (broad singlet). Coupling constants (J) are in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Measured melting points are uncorrected. Boiling points were measured at 0.8 mmHg unless otherwise specified herein. LC-MS data were acquired on Agilent 1200 HPLC system equipped with DAD/ELSD/LCMS-6120 diode-matrix and mass-selective detector, column: Poroshell 120 SB-C18, 4.6 mm × 30 mm. Eluent, A, acetonitrile–water with 0.1% of FA (99 : 1); B, water with 0.1% of FA. Optical rotations were measured on polarimeter in methanol using 1 dm cell; optical rotation values are given in 10^{-1} deg cm^2 g^{-1}; concentrations (c) are given in mmol L^{-1}, wavelength 589 nm at 20 °C. The enantiomeric excess and retention time (t_R) was determined for major signal by HPLCs: Daicel CHIRALPACK IA, 5 μm, 4.6 × 250 mm, Daicel CHIRALPACK IB, 5 μm, 4.6 × 250 mm, Daicel CHIRALPACK OJ-H, 5 μm, 4.6 × 250 mm, Daicel CHIRALPACK AS-H, 5 μm, 4.6 × 250 mm chiral columns, injection volume 0.1 μL, eluent (hexanes: 2-propanol). Solid compounds were recrystallized from acetonitrile unless other is specified.

Synthesis of 3,4-disubstituted isoxazoles, representative procedure

Methyl 3-(((*tert*-butoxycarbonyl)amino)methyl)isoxazole-4-carboxylate (Boc-1A-CO_2Me). A 250 mL round bottomed flask was charged with a magnetic stirrer, corresponding chloroxime **1** (2 g, 9.6 mmol) and EtOAc (20 mL). To the resulting vigorously stirred homogeneous solution (*E*)-methyl 3-(dimethylamino) acrylate **8** (1.48 g, 11.5 mmol) was added followed by addition of $NaHCO_3$ (1.6 g, 19.2 mmol) at the ambient temperature. The resulting mixture was stirred overnight. The progress of the reaction was monitored by NMR spectroscopy. After the reaction was complete, the organic phase was washed with 10% $NaHSO_{4(aq)}$ (3 × 5 mL), 10% $K_2CO_{3(aq)}$ (2 × 5 mL) and brine (1 × 5 mL). Organic phase was dried over anhydrous Na_2SO_4. The resulting mixture was filtered through a silicagel pad and concentrated to yield **Boc-1A-CO_2Me** (95%, 2.3 g) as a beige powder, mp 65 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ 9.59 (s, 1H, *isoxaz*), 7.24 (brs, 1H, *NH*), 4.41 (d, 2H, CH_2), 3.80 (s, 3H, OCH_3), 1.39 (s, 9H, CH_3-*Boc*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.9, 161.1, 160.0, 155.4, 111.9, 78.2, 51.9, 35.9, 28.1. MS (APCI) m/z [M − Boc + 1H]$^+$ calculated for $C_{10}H_{13}N_2O_5$: 255.1; found: 255.4. Anal. calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.35; H, 6.07; N, 10.52.

Synthesis of 3,5-disubstituted isoxazoles, representative procedure

Methyl 3-(((*tert*-butoxycarbonyl)amino)methyl)isoxazole-5-carboxylate (Boc-1B-CO_2Me). A 250 mL round bottomed flask was charged with a magnetic stirrer, corresponding chloroxime **1** (2 g, 9.6 mmol) and EtOAc (20 mL). Then, the resulting vigorously stirred homogeneous solution was cooled to −5–0 °C and methyl propiolate (0.9 mL, 10.1 mmol) was added followed by addition of $NaHCO_3$ (1.6 g, 19.2 mmol) (in case of reaction **7** (2 g, 7.6 mmol) with ethynyltrimethylsilane **12** (5.4 mL, 38 mmol) dropwise addition of Et_3N (1.6 mL, 11.5 mmol) as a solution in EtOAc (100 mL) was required). The resulting mixture was stirred overnight. The progress of the reaction was

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monitored by NMR spectroscopy. Work-up was done by simple filtration through silica pad, then the resulting solution was concentrated and dried *in vacuo* to yield the corresponding product **Boc-1B-CO_2Me** (89%, 2.2 g) as a white powder, mp 84–86 °C. For reaction of compound **7** with **12** when the reaction was complete, the organic phase was washed with 10% $K_2CO_{3(aq)}$ (2 × 20 mL) and brine (1 × 20 mL). Organic phase was dried over anhydrous Na_2SO_4. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.49 (s, 1H, *NH*), 7.05 (s, 1H, *isoxaz*), 4.24–4.23 (d, 2H, $J = 5.5$, CH_2), 3.89 (s, 3H, OCH_3), 1.39 (br, 9H, CH_3-*Boc*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.7, 159.5, 156.7, 155.7, 109.0, 78.5, 52.9, 35.6, 28.1. MS (APCI) m/z [M − Boc + 1H]$^+$ calculated for $C_{10}H_{13}N_2O_5$: 255.1; found: 255.4. Anal. calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.27; H, 6.54; N, 10.63.

Representative procedure for cleavage of *tert*-butyloxycarbonyl group

1-(3-(Aminomethyl)isoxazol-4-yl)ethan-1-one hydrochloride (1A-COMe·HCl). A 250 mL round bottomed flask was charged with a magnetic stirrer, corresponding Boc-protected isoxazole **Boc-1A-COMe** (2.5 g, 9.8 mmol) and EtOAc (25 mL). The flask was submerged into an ice cooling bath; and to the vigorously stirred homogeneous solution equimolar ratio of MeOH (1.05 eq.) was added followed by dropwise addition of AcCl (1.05 eq.). As the result white precipitate was formed. After the reaction was complete (NMR control) resulting solid was filtered and washed with cold EtOAc and recrystallized from MeCN (if it was necessary) affording **1A-COMe·HCl** as a white powder. In case of EWG = CO_2Me-group AcCl (1.05 eq.) in MeOH was used.

1A-COMe·HCl: 95%, white powder, mp 94–96 °C. ^{1}H NMR (500 MHz, D_2O-d_2): δ 9.53 (s, 1H, *isoxaz*), 4.54 (s, 2H, CH_2), 2.60 (s, 3H, CH_3-Ac). ^{13}C NMR (125 MHz, DMSO-d_6): δ 192.0, 166.1, 155.9, 119.8, 34.4, 29.0. MS (APCI) m/z [M + 1H]$^+$ calculated for $C_6H_9N_2O_2$: 141.1; found: 141.2. Anal. calcd for $C_6H_9ClN_2O_2$: C, 40.81; H, 5.14; N, 15.86. Found: C, 40.25; H, 5.33; N, 15.96.

Representative procedure for the hydrolysis of isoxazole-based esters

3-(((*tert*-Butoxycarbonyl)amino)methyl)isoxazole-4-carboxylic acid (Boc-1A-CO_2H). A 250 mL round bottomed flask was charged with a magnetic stirrer, corresponding isoxazole (**Boc-1A-CO_2Me**, 2 g, 7.8 mmol) and MeOH (18 mL). Next, the flask was submerged into an ice cooling bath and to the resulting vigorously stirred homogeneous solution 2 equiv. of 10% $NaOH_{(aq)}$ was added dropwise. After the NMR control indicated the reaction completion (10–24 h), the solution was concentrated *in vacuo*. $HCl_{(aq)}$, or $NaHSO_{4(aq)}$, was added dropwise until pH = 3 was reached and solid NaCl was added until the resulting solution become saturated. The product was extracted by EtOAc (3 × 20 mL). Combined organic fractions were dried over anhydrous $MgSO_4$, concentrated and dried *in vacuo* yielding **Boc-1A-CO_2H** as a white powder, (95%, 1.8 g), mp 129–131 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.25 (br, 1H, C–OOH), 9.45 (s, 1H, *isoxaz*), 7.17 (brs, 1H, *NH-major rotamer*), 6.80 (brs, *NH-minor of rotamer*), 4.40 (d, 2H, $J = 4.5$, CH_2), 1.38 (s, 9H, CH_3-*Boc*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.6, 162.4, 160.3, 155.5, 113.2, 78.2, 36.1, 28.2. MS (APCI) m/z [M − 1H]$^+$ calculated for $C_{10}H_{13}N_2O_5$: 241.1; found: 241.2. Anal. calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.56. Found: C, 49.38; H, 5.66; N, 11.43.

Representative procedure for the for the synthesis of 3-substituted isoxazoles

***tert*-Butyl (isoxazol-3-ylmethyl)carbamate (Boc-1-H).** A round bottomed flask (100 mL) was charged with a magnetic stirrer, substrate **Boc-1-H-TMS** (5.5 g, 20.3 mmol) and MeOH (25 mL). KHF_2 5 mol% (80 mg, 1 mmol) with $H_2O_{(cat)}$ (100 μL) were added and the resulting homogeneous solution was vigorously stirred for 24 h at the ambient temperature while the progress was monitored by NMR spectroscopy. After the reaction was completed the solvent was evaporated and the remaining residue was dissolved in EtOAc (50 mL). Organic phase was filtered through anhydrous Na_2SO_4 pad and concentrated to yield **Boc-1-H** as a white powder (94%, 3.8 g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.79 (m, 1H, *CH–isoxaz*), 7.43–7.35 (brs, 1H, *NH*), 6.42 (s, 1H, *isoxaz*), 4.20–4.19 (m, 2H, CH_2), 1.39 (s, 9H, CH_3-*Boc*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.5, 159.8, 155.7, 103.8, 78.3, 35.5, 28.2. Anal. calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.36; H, 7.18; N, 14.01.

Synthesis of the ABT-418 bioisostere 16

***tert*-Butyl (2*S*)-2-(5-(bromomethyl)-4,5-dihydroisoxazol-3-yl) pyrrolidine-1-carboxylate (13).** A 500 mL round bottomed flask was charged with a magnetic stirrer, corresponding chloroxime **4** (10 g, 40.2 mmol) and EtOAc (100 mL). To the resulting vigorously stirred homogeneous solution allyl bromide (5.6 g, 46.23 mmol) was added followed by addition of $NaHCO_3$ (6.7 g, 80.4 mmol). The resulting mixture was stirred overnight. The progress of the reaction was monitored by NMR spectroscopy. After the reaction was complete, organic phase was dried over anhydrous Na_2SO_4 and filtered through the silica gel pad. The resulting solution was concentrated to yield **13** (95%, 12.95 g) as a white powder, mp 60 °C.

13-*S*-Isomer: 95%, white powder, $[\alpha]_D^{20} = -80.00$ ($c = 35.42$). 99.6% ee, $t_R = 12.2$ min;

13-*R*-Isomer: 97%, white powder, $[\alpha]_D^{20} = +81.84$ ($c = 35.42$), 99.8% ee, $t_R = 10.5$ min.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.85–4.78 (m, 1H, *isoxazoline–CH*), 4.63 (brs, 1H, *–pyrrolidine–CH*), 3.48–3.32 (m, 4H, CH_2–*pyrrolidine* + CH_2–*Br*), 2.94–2.90 (m, 2H, CH_2–*isoxazoline*), 2.17–1.91 (m, 4H, CH_2–*pyrrolidine*), 1.46 (s, 9H, CH_3-*Boc*). ^{13}C NMR (125 MHz, DMSO-d_6, mixture of both rotamers): δ 160.3, 159.7, 153.5, 153.1, 78.8, 78.3, 54.0, 46.3, 46.0, 38.7, 35.7, 35.2, 34.8, 30.4, 30.2, 29.6, 29.3, 28.0, 23.9, 23.0. MS (APCI) m/z [M − Boc]$^+$ calculated for $C_8H_{13}BrN_2O$: 235.0; found: 235.1. Anal. calcd for $C_{13}H_{21}BrN_2O_3$: C, 46.86; H, 6.35; N, 8.41. Found: C, 46.77; H, 6.44; N, 8.57.

***tert*-Butyl (*S*)-2-(5-methylisoxazol-3-yl)pyrrolidine-1-carboxylate (14).** A 250 mL round bottomed flask was charged with a magnetic stirrer, corresponding isoxazoline **13** (12.5 g, 37.5 mmol) and DMF (50 mL). K_2CO_3 (10.4 g, 75 mmol) was added and the resulting mixture was stirred overnight at 100 °C. The progress of the reaction was monitored by NMR spectroscopy.

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After the reaction was complete, the reaction mixture was concentrated the residue was poured into ice-bath and aqueous phase was extracted with EtOAc. The combined orhanic phases were washed with brine (4 × 20 mL). Organic phase was dried over anhydrous Na_2SO_4. The resulting mixture was filtered through the silicagel pad and the solution was concentrated. The residue is colorless oil which was solidified upon standing 77%.

14-*S*-Isomer: 77%, $[\alpha]_D^{20} = -78.8$ ($c = 3.96$), 99.9% ee, $t_R = 9.5$ min;

14-*R*-Isomer: 75%, $[\alpha]_D^{20} = +79.63$ ($c = 3.96$), 99.9% ee, $t_R = 7.6$ min.

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.10 (brs, 1H, *isoxaz*), 4.83–4.77 (m, 1H, *CH–pyrrolidine*), 3.43–3.38 (m, 2H, *CH$_2$–pyrrolidine*), 2.36 (s, 3H, *CH$_3$*), 2.21 (br, 1H, *CH–pyrrolidine*), 1.85 (br, 3H, *CH–pyrrolidine*), 1.39, (s, 9H, *CH$_3$-Boc*, *major rotamer*), 1.24 (s, 9H, *CH$_3$-Boc*, *minor rotamer*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.02, 166.4, 166.0, 153.5, 153.2, 100.4, 99.8, 78.6, 78.5, 53.3, 53.1, 46.3, 46.0, 32.6, 31.3, 28.1, 27.9, 23.6, 22.9, 11.7.

MS (APCI) m/z $[M + 3H]^+$ calculated for $C_{13}H_{23}N_2O_3$: 255.3; found: 255.2. Anal. calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.95; H, 7.83; N, 11.14.

(*S*)-5-Methyl-3-(pyrrolidin-2-yl)isoxazole hydrochloride (15·HCl). The same experimental procedure as previously described for 3,4- and 3,5-analogues for the cleavage of Boc-group was used.

15-*S*-Isomer, white powder, 92%, $[\alpha]_D^{20} = -21.63$ ($c = 53.00$);

15-*R*-Isomer, white powder, 93%, $[\alpha]_D^{20} = +22.95$ ($c = 53.00$).

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.63 (br, 1H, *NH·HCl*), 9.57 (br, 1H, *NH·HCl*), 6.55 (s, 1H, *isoxaz*), 4.66 (brs, 1H, *CH*), 3.27–3.22 (m, 2H, *CH$_2$–pyrrolidine*), 2.43 (s, 3H, *CH$_3$*), 2.35–2.33 (m, 1H, *CH–pyrrolidine*), 2.02 (br, 3H, *CH$_2$–pyrrolidine*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.6, 160.1, 101.4, 54.0, 44.4, 29.4, 22.8, 11.9. MS (APCI) m/z $[M - Cl + H]^+$ calculated for $C_8H_{19}N_2O$: 153.1; found: 153.2. Anal. calcd for $C_8H_{13}ClN_2O$: C, 50.93; H, 6.95; N, 14.85. Found: C, 50.87; H, 7.08; N, 14.89.

(*S*)-5-Methyl-3-(1-methylpyrrolidin-2-yl)isoxazole (16). A 500 mL round bottomed flask was charged with magnetic stirrer and corresponding isoxazole **15** (2.1 g, 10.60 mmol) which was suspended in dichloroethane (250 mL). MeOH (50 mL) was added followed by addition of 30% $CH_2O_{(aq)}$ (10 mL) and $NaBH(OAC)_3$ (7.0 g, 33.03 mmol). Then, the resulting mixture was stirred overnight at the ambient temperature. Next, the reaction mixture was concentrated, EtOAc (250 mL) was added and K_2CO_3 was added until the pH = 10 was reached (**Caution**: carbon dioxide evolution!). The reaction mixture was then stirred over Na_2SO_4 for *ca.* 10 min filtered and concentrated. The product was purified by distillation yielding **16** (1.52 g, bp 75–80 °C at 5.5 mmHg) as a colorless liquid (with pyrrolidine odour) which is extremely well soluble in water.

16-*S*-Isomer, 82%, $[\alpha]_D^{20} = -8.00$ ($c = 60.16$);

16-*R*-Isomer, 83%, $[\alpha]_D^{20} = +7.86$ ($c = 60.16$).

^{1}H NMR (500 MHz, DMSO-d_6): δ 6.14 (brs, 1H, *isoxaz*), 3.24–3.19 (t, 1H, $J = 10.0$, *CH–pyrrolidine*), 3.07–3.03 (m, 1H, *CH–pyrrolidine*), 2.36 (s, 3H, *CH$_3$–NH*), 2.26–2.19 (m, 1H, *CH–pyrrolidine*), 2.11 (s, 4H, *CH$_3$ + CH*), 1.84–1.71 (m, 3H, *CH–pyrrolidine*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.1, 166.1, 99.7, 61.3, 56.0, 31.7, 22.4, 11.8. MS (APCI) m/z $[M + H]^+$ calculated for $C_9H_{15}N_2O$: 167.1; found: 167.2. Anal. calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 65.14; H, 8.33; N, 16.94.

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