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A bio-inspired approach to proline-derived 2,4-disubstituted oxazoles

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Abstract: A convenient four-step approach to the synthesis of (*S*)-4-alkyl-2-(pyrrolidin-2-yl)oxazoles starting from L-Boc-proline inspired by naturally occurring oxazole-containing peptidomimetics is described. The key step is the cyclization of 1-Boc-*N*-(1-oxoalkan-2-yl)pyrrolidine-2-carboxamides – aldehyde intermediates which demonstrate low to moderate stability – under Appel reaction conditions. This method furnishes the target compounds with more than 98% *ee* and in a 17–51% overall yield and has been used at up to a 45-g scale.

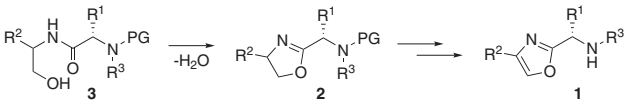
Keywords: conformational restriction; heteroaliphatic; lead-oriented synthesis; oxazoles; peptidomimetics; synthesis.

Introduction

Since their isolation from marine products in the late 1980s, oxazole-containing peptidomimetics have been studied extensively by synthetic organic and medicinal chemists [1–5]. It is believed that many of these natural products are derived from enzymatic post-translational modifications of peptide-based precursors containing serine or threonine moieties [2]. It is not surprising, therefore, that 2,4-disubstituted oxazoles of general formula **1** derived from α-amino acids have attracted much attention as promising building blocks for drug discovery [6–13] or total synthesis of natural products including plantazolicins [14, 15], telomestatin [16], ulapualides [17, 18] and diazonamide A [19, 20] and as ligands for enantioselective catalysis [21, 22]. In most cases, a 'biomimetic' approach to the synthesis of **1** has been used, including the formation of oxazoline **2** and its subsequent aromatization (Scheme 1) [7–23]. However, this method is effective only when the substituent R^1 in the oxazole ring formed is an electron-withdrawing group (e.g. $R^1 = CO_2Me$). Even for $R^1 = Ph$, the aromatization step requires harsh conditions (NiO_2, 150°C, μW) [13]. Recently, an alternative approach has been reported for the preparation of the compounds **1** with primary amino group ($R^3 = H$), which is based on oxidation of phthaloyl derivatives of the type **3** ($R^1 = H$, Ph, Bn; $R^2 = i$-Pr; R^3/PG = phthaloyl) with the Dess-Martin reagent, followed by cyclodehydration and deprotection [6]. Apart from the limited scope, the method offers a moderate yield of the key step (34–50%) and can be used only at a milligram scale. Moreover, partial racemization occurs upon removal of the phthalimide protective group.

In this work, we have taken inspiration from the 'biocore' concept described by Kombarov and co-workers [24]. This concept refers to a combination of (hetero)aliphatic and hydrophilic aromatic rings providing privileged structures for drug discovery (Figure 1). Analysis of the literature data published on 'biocores' obtained by a combination of oxazole and common heteroaliphatic amines (pyrrolidine/piperidine) shows that 2-(2-pyrrolidinyl)oxazoles **4** are most often encountered in papers and patents [25]. As in the case of the general structure **1**, however, nearly all known compounds **4** are substituted with R^1 = aryl or CO_2R, or are derived from them [7–12, 21–23].

Here, we describe the multigram synthesis of oxazole-substituted pyrrolidines **4** with aliphatic substituents at C-4 position ($R^1 = H$, alkyl; $R^2 = H$) starting from enantiopure (*S*)-*N*-Boc-proline (**5** in Figure 1) [26]. Instant JChem was used for the prediction of the physico-chemical properties of the compounds. Conformational restriction provided by the saturated heteroaliphatic ring of **4** and an improved hydrophilicity are valuable features in lead-oriented synthesis in medicinal chemistry [27, 28].



Scheme 1 Biomimetic approach to oxazole building blocks.

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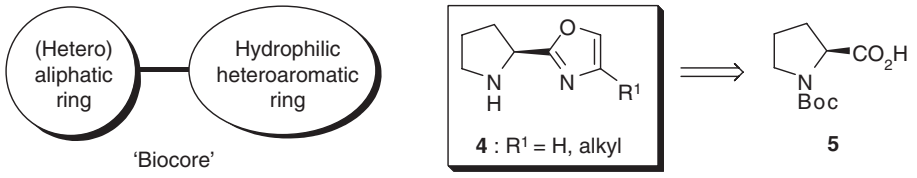
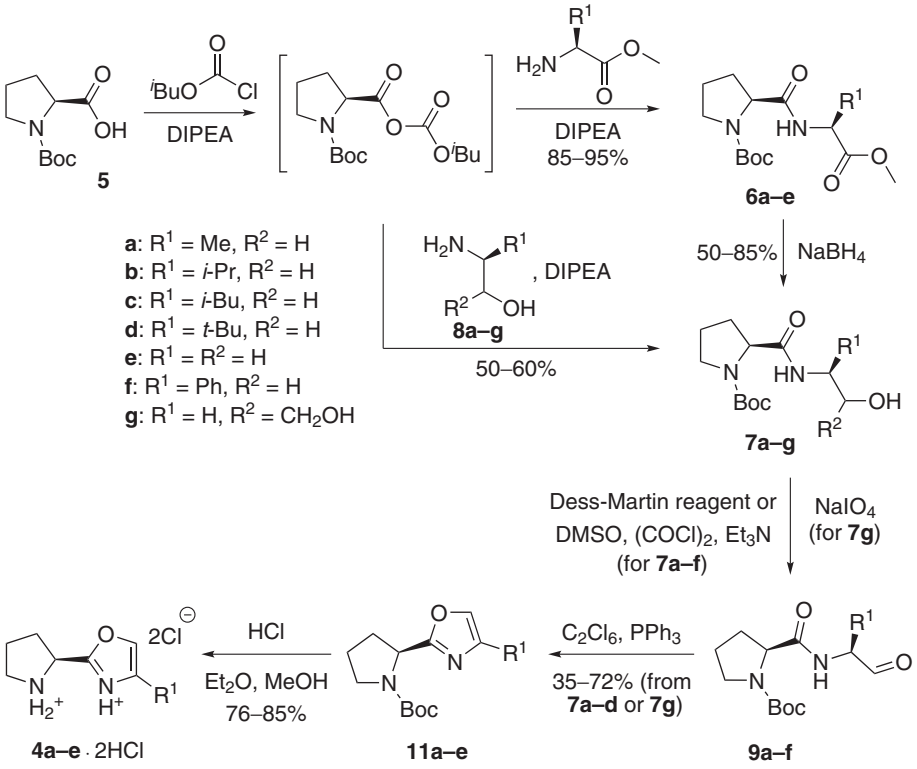


Figure 1 'Biocore' concept and its implementation into the target compounds **4**.

Results and discussion

Our strategy for the preparation of the secondary amines **4a–e** was related to the 'biomimetic' approaches shown in Scheme 1. Initially, the synthesis followed the literature analogs and involved dipeptides **6**, which were prepared from **5** in an 85–95% yield using the mixed anhydride activation method (Scheme 2) [29]. However, reduction of **6a–e** with $NaBH_4$ was accompanied by a problematic isolation of the target products **7a–e**, which was related to their high aqueous solubility and formation of stable boron complexes. Although compounds **7** were isolated in a 50–85% yield, the attempted scaling up of this procedure was not successful. Therefore, we switched to a one-step synthesis of **7** directly from **5** using coupling with β-amino alcohols **8** (either commercially available or prepared from the corresponding α-amino acids). Products **7a–f** were obtained with overall yields of 60–86%. The procedure did not require chromatographic purification and was amenable to a multigram scale-up.

The next step, oxidation of **7** to aldehydes **9**, was performed first with the Dess-Martin reagent, by analogy with the literature examples [6, 29] and our previous in-house experience. It was found that in the case of **7a**, the yield of the product **9a** varied significantly in different experiments [35–70% by ^{1}H nuclear magnetic resonance (NMR)]. Moreover, the product **9a** showed limited storage stability. A detailed investigation revealed that the Swern reaction [dimethyl sulfoxide (DMSO), $(COCl)_2$, Et_3N, –60°C, 1 h] gives more reproducible results, and the crude products **9a–d** were obtained in a 55–85% yield (by ^{1}H NMR). In the case of **7e** (R^1 = H), the use of the Dess-Martin reagent appeared to be more fruitful than the Swern oxidation (35% vs. 5% yield of **9e** by ^{1}H NMR). Unfortunately, the



Scheme 2 Synthesis of the compounds **4a–e** · 2HCl.

product **9f** (R^1 = Ph) could not be obtained at all using either method.

It was shown that the storage stability of products **9a–e** is strongly affected by the steric volume of the substituent R^1. In particular, the product **9a** has limited stability in CH_2Cl_2 solution (ca. 1 h) and as a neat product at –24°C (ca. 8 h). On the contrary, compounds **9b–d** with relatively bulky alkyl substituents are relatively stable in both cases (at least for 24 h). The product **7e** is rather unstable either in CH_2Cl_2 solution or as a neat compound at –24°C (less than 1 h). Other factors influencing the stability of **9a–e** include temperature which should be kept below 20°C during all manipulations with **9** including the evaporation of the solvent. It can be suggested that the stability of the products **9a–f** is also related to their reactivity toward self-condensation, which is diminished upon an increase in the size of the alkyl substituent R^1. In the case of R^1 = Ph, this side reaction becomes especially fast, presumably due to a concomitant increase in the acidity of α-CH adjacent to the aldehyde moiety. It was apparent that the use of acidic or basic reagents should be avoided during the synthesis of **9e**, which might improve the yield of this product. For this reason, we have synthesized amide **7g** (60% yield) and subjected it to oxidative cleavage with $NaIO_4$. Using this procedure, the product **9e** was obtained in a 45% yield.

Taking into account the low stability of aldehydes **9**, the crude products **9** were used immediately in the next step, which is the dehydrative oxazole ring formation. The Appel reaction was used for this reason, by analogy with the literature results published previously [6, 29]. It was found that the use of the CBr_4-PPh_3 system gave a low yield of the target products **11** (less than 20% by ^{1}H NMR), whereas with C_2Cl_6-PPh_3, the oxazoles **11a–e** were obtained in a 50–90% yield.

The structure of compound **11a** was confirmed by X-ray single crystal analysis (CCDC-1570445 [30], Figure 2). It should be noted that only one enantiomer of **11a** was observed in the crystal structure.

In the final step of the synthesis, deprotection of compounds **11a–e** was performed by treatment with HCl. It was found that using a solution of HCl in Et_2O resulted in precipitation of **11** · HCl, so that a complete conversion could not be achieved. Fortunately, the use of HCl in Et_2O-MeOH furnished the target products **4a–e** as dihydrochlorides in a 76–85% yield. It should be noted that the method can be used for the synthesis of up to 45 g of the products **4** · 2HCl in a single run.

To analyze the optical purity of the products, compound **4a** · 2HCl was derivatized with the Mosher's reagent, which gave a single diastereomer according to

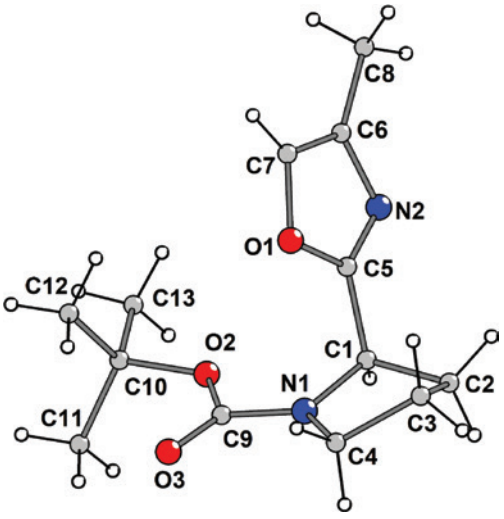


Figure 2 Molecular structure of compound **11a**.

^{1}H NMR and ^{19}F NMR analyses. In addition, the enantiomer of compound **11c** was synthesized from D-*N*-Boc-proline and used as a control for chiral stationary phase high-performance liquid chromatography (HPLC). It was found that enantiopure product **11c** showed no detectable peak of its enantiomer in the chromatogram [≥98% *ee*, (ChiralPack® IA column, hexanes – 2-propanol (95:5) as an eluent]. Under the same conditions, single peaks (≥98% *ee*) were also observed in the chromatograms of other products **11**.

Conclusions

Synthesis of (*S*)-4-alkyl-2-(pyrrolidin-2-yl)oxazoles was performed starting from L-Boc-proline and using an approach inspired by biosynthesis of oxazole-containing peptidomimetics isolated from natural products. Optimization of the procedures was performed for each step, in order to make the method scalable. It was shown that the key intermediates, 1-Boc-*N*-(1-oxoalkan-2-yl)pyrrolidine-2-carboxamides (**9**), demonstrate low to moderate stability, which is increased with the increasing size of the alkyl group near the aldehyde moiety. Therefore, it is strongly recommended to submit them to the next step immediately after isolation.

The target products were obtained in only four steps from derivatives of natural α-amino acids in a 17–51% overall yield, with ≥98% *ee* and at up to a 45-g scale. The overall yield of the product is increased upon an increase in the lipophilicity of the compound and hence follows the 'LogP drift' effect proposed by Churcher and co-workers (Figure 3) [27]. In our opinion, this effect might be

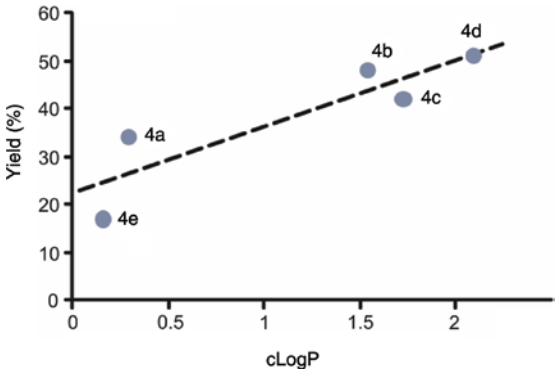


Figure 3 Overall yields of products **4a–e** · 2HCl as a function of their lipophilicity.

related to isolation issues observed for more hydrophilic compounds.

In conclusion, (*S*)-4-alkyl-2-(pyrrolidin-2-yl)oxazoles can be considered as building blocks readily available to the chemical community. We believe that synthetic accessibility and favorable physico-chemical characteristics of these oxazole-derived 'biocores' make them valuable starting points for early drug discovery.

Experimental

Solvents were purified according to standard procedures [31]. Compounds **6a–e** [29], **8b–d** and **8f** [32] were prepared using reported methods. All other starting materials were purchased from commercial sources. Analytical thin-layer chromatography (TLC) was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C). Signal assignments for compounds **4a–e** · 2HCl were made using ^{1}H-^{1}H correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond correlation (HMBC) experiments. Mass spectra were recorded on an Agilent 1100 LC/MSD SL instrument [atmospheric pressure electrospray ionization (APESI)]. The stability of aldehydes **9** in CH_2Cl_2 solution or as neat products at –24°C was studied by recording ^{1}H NMR spectra for the aliquots hourly; the compound was assumed to be stable if the relative intensity of the aldehyde signal changed by no more than 10%.

General procedure for synthesis of amides 7a–g

Isobutyl chloroformate (41.2 g, 0.30 mol or methyl chloroformate) was added dropwise to a solution of L-Boc-proline (65.0 g, 0.30 mol) and *N,N*-diisopropylethylamine (DIPEA) (42.6 g, 0.33 mol) in anhydrous CH_2Cl_2 (1200 mL) at 0°C. After 1 h at room temperature, the mixture was cooled to –15°C and then amino alcohol **8** (0.33 mol) and DIPEA (42.6 g, 0.33 mol) were added in one portion. The mixture was slowly warmed to room temperature and stirred overnight. The volatiles were removed under reduced pressure, and the solid residue was triturated with Et_2O (400 mL), filtered, washed with Et_2O (200 mL) and then with H_2O (100 mL). As the product is water soluble, it is necessary to use a minimal amount of H_2O at this step. The product **7** was dried under reduced pressure.

***tert*-Butyl (*S*)-2-[((*S*)-1-hydroxypropan-2-yl)carbamoyl]-pyrrolidine-1-carboxylate (7a)** Yield 62.9 g (63%); white solid; mp 175–178°C; MS: *m/z* 295 (MNa^+); ^{1}H NMR ($CDCl_3$): δ 6.82 (br s, 0.68H, NH) and 6.23 (br s, 0.32H, NH), 4.24 (br s, 1H), 4.02 (br s, 1H), 3.78–3.58 (m, 1H), 3.58–3.24 (m, 4H), 2.35–1.74 (m, 4H), 1.46 (s, 9H), 1.15 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 172.1, 155.3, 80.3, 66.1, 60.8 and 59.9, 47.5, 46.8, 30.9, 28.1, 24.3 and 23.5, 16.7. Anal. Calcd for $C_{13}H_{24}N_2O_4$: C, 57.33; H, 8.88; N, 10.29. Found: C, 57.06; H, 8.77; N, 10.19.

***tert*-Butyl (*S*)-2-[((*S*)-1-hydroxy-3-methylbutan-2-yl)carbamoyl] pyrrolidine-1-carboxylate (7b)** Yield 96.7 g (86%); white solid; mp 112–115°C; MS: *m/z* 301 (MH^+); ^{1}H NMR ($CDCl_3$): δ 6.93 (br s, 0.77H) and 6.28 (br s, 0.33H), 4.30 (br s, 1H), 3.75–3.65 (m, 2H), 3.59 (br s, 1H), 3.52–3.27 (m, 2H), 3.24–2.43 (m, 1H), 2.40–1.65 (m, 5H), 1.46 (s, 9H), 0.93 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 172.2, 155.4 and 154.3, 80.3, 63.3, 61.0 and 60.0, 56.8, 46.8, 30.8, 28.6 and 28.1, 24.3 and 23.5, 19.4, 18.1. Anal. Calcd for $C_{15}H_{28}N_2O_4$: C, 59.97; H, 9.40; N, 9.33. Found: C, 59.80; H, 9.61; N, 9.10.

***tert*-Butyl (*S*)-2-[((*S*)-1-hydroxy-4-methylpentan-2-yl)carbamoyl] pyrrolidine-1-carboxylate (7c)** Yield 76.2 g (82%); white solid; mp 99–102°C; MS: *m/z* 337(MNa^+), 315 (MH^+); ^{1}H NMR ($CDCl_3$): δ 6.75 (br s, 0.66H) and 6.17 (br s, 0.34H), 4.23 (br s, 1H), 3.97 (br s, 1H), 3.62 (br s, 1H), 3.56–2.89 (m, 4H), 2.33–1.73 (m, 4H), 1.65–1.52 (m, 1H), 1.44 (s, 9H), 1.38–1.21 (m, 2H), 0.89 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 172.1, 155.3 and 154.21, 80.3, 65.5, 60.8 and 60.0, 49.9, 46.8, 39.8, 30.8, 28.1, 24.6 and 23.5, 22.9, 21.8. Anal. Calcd for $C_{16}H_{30}N_2O_4$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.07; H, 9.49; N, 9.01.

***tert*-Butyl (2*S*)-2-[(1-hydroxy-3,3-dimethylbutan-2-yl)carbamoyl] pyrrolidine-1-carboxylate (7d)** Yield 90.4 g (84%); white solid; mp 122–125°C; MS: *m/z* 337 (MNa^+), 315 (MH^+); ^{1}H NMR ($CDCl_3$): δ 6.99 (br s, 0.85H) and 6.27 (br s, 0.15H), 4.33 (br s, 1H), 3.91–3.68 (m, 2H), 3.60–3.23 (m, 3H), 2.84 (s, 0.77H) and 2.53 (s, 0.23H), 2.43–1.81 (m, 4H), 1.47 (s, 9H), 0.92 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 172.3, 155.5, 80.4, 62.7, 61.1, 60.0 and 59.6, 46.9, 33.1, 30.7, 28.1, 26.6, 24.4. Anal. Calcd for $C_{16}H_{30}N_2O_4$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.74; H, 9.92; N, 8.95.

***tert*-Butyl (S)-2-[(2-hydroxyethyl)carbamoyl]pyrrolidine-1-carboxylate (7e)** Yield 63.0 g (65%); white solid; mp 157–159°C (lit. [33] mp 157–158°C). All other spectral and physical data are in accordance with the literature.

***tert*-Butyl (*S*)-2-[((*S*)-2-hydroxy-1-phenylethyl)carbamoyl]pyrrolidine-1-carboxylate (7f)** Yield 85.2 g (78%); white solid; mp 121–124°C; MS: *m/z* 334 (MH^+); ^{1}H NMR ($CDCl_3$): δ 7.54 (br s, 0.45H) and 6.74 (br s, 0.55H), 7.48–6.97 (m, 5H), 5.05 (br s, 1H), 4.45–4.12 (m, 1H), 4.00–3.66 (m, 2H), 3.59–3.06 (m, 2H), 2.95 (br s, 1H), 2.50–1.65 (m, 4H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 172.4, 156.0 and 154.8, 139.1, 128.7, 127.6, 126.7 and 126.6, 80.7 and 80.6, 66.4 and 66.1, 61.2 and 60.2, 55.7, 47.1, 30.9, 28.3, 24.6 and 23.8. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.50; H, 7.69; N, 8.37.

***tert*-Butyl (2*S*)-2-[(2,3-dihydroxypropyl)carbamoyl]pyrrolidine-1-carboxylate (7g)** The product was obtained according to

the general procedure except for the work-up step. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography using $CHCl_3$/MeOH (14:1) as an eluent to give the pure compound as a clear viscous oil which solidified overnight: yield 25.6 g (60%); white crystals; mp 95–97°C; R_f 0.38 [$CHCl_3$/MeOH (14:1)]; ^{1}H NMR ($CDCl_3$): δ 7.16 (br s, 0.6H) and 6.97 (s, 0.4H), 4.26–4.10 (m, 1H), 4.08–3.78 (m, 2H), 3.78–3.66 (m, 1H), 3.56–3.19 (m, 6H), 2.31–1.60 (m, 4H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 174.5 and 173.9, 155.5 and 154.7, 80.7, 70.8, 63.6, 61.1 and 60.3, 47.2, 42.0, 31.2, 29.3 and 28.3, 24.5 and 23.7. Anal. Calcd for $C_{13}H_{24}N_2O_5$: C, 54.15; H, 8.39; N, 9.72. Found: C, 54.49; H, 8.62; N, 9.34. MS (CI): 289 (MH^+).

General procedure for synthesis of aldehydes 9a–e

Method A A suspension of alcohol **7** (0.12 mol) in CH_2Cl_2 (100 mL) was added in small portions to a solution of the Dess-Martin reagent (60.6 g, 0.14 mol) and *t*-BuOH (9.70 g, 0.13 mol) in CH_2Cl_2 (800 mL) at 0°C. Then the mixture was allowed to warm to room temperature, and after the reaction was complete, as monitored by TLC, about 1 h, the excess of the Dess-Martin reagent was neutralized with a solution of $Na_2S_2O_3$ (20 g) in saturated aqueous $NaHCO_3$ (400 mL) with stirring. After an additional 10 min of stirring, the mixture was transferred into a separatory funnel. The organic phase was separated, washed with brine (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product **9a–e** which was immediately used in the next step without purification. The temperature should be kept below 20°C during all manipulations with the product, including the evaporation of the solvent.

Method B A solution of DMSO (28.7 g, 0.37 mol) in CH_2Cl_2 (80 mL) was added dropwise to a solution of oxalyl chloride (22.3 g, 0.18 mol) in CH_2Cl_2 (1100 mL) at −60°C. The mixture was stirred for 20 min at the same temperature and then treated with a suspension of alcohol **7** (0.15 mol) in CH_2Cl_2 (100 mL) at −60°C. The solution was stirred for an additional 30 min at −60°C, then Et_3N (79.9 g, 0.73 mol) was added and the mixture was allowed to warm to 15°C. Water (250 mL) was added, the mixture was stirred for 5 min and the organic phase was separated. The aqueous phase was washed with CH_2Cl_2 (150 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude compound which was immediately used in the next step without purification. The temperature should be kept below 20°C during all manipulations with the product, including the evaporation of the solvent. For comparative analysis of the methods A and B, see the main text.

tert-Butyl (*S*)-2-[(2-oxoethyl)carbamoyl]pyrrolidine-1-carboxylate (9e) (alternative procedure)

$NaIO_4$ (37.2 g, 0.17 mol) was added in portions to a stirred solution of diol **7g** (25.0 g, 0.087 mol) in tetrahydrofuran (THF) (250 mL) and H_2O (250 mL) at 5–10°C. After stirring at 20°C for 1 h, the mixture was extracted with Et_2O (4 × 150 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The temperature should be kept below 20°C during all manipulations with the product, including the evaporation of the solvent. The crude product **9e** was immediately used in the next step without purification.

General procedure for synthesis of oxazoles 11a–e

Ph_3P (115.5 g, 0.44 mol) was added to a stirred solution of C_2Cl_6 (104.3 g, 0.44 mol) in dry MeCN (1200 mL). The mixture was cooled to 0°C and treated with Et_3N (89.0 g, 0.88 mol). The mixture was kept at this temperature for 10 min, and a solution of aldehyde **9** (0.15 mol) in dry MeCN (100 mL) was added in small portions, with the temperature kept between 0 and 10°C. The resulting mixture was stirred at room temperature for 14 h. The solvent was evaporated and the residue was triturated with Et_2O (400 mL). The precipitate was filtered, washed with saturated aqueous $NaHCO_3$ (to pH ~ 8) and then with Et_2O (2 × 200 mL). The organic layer was separated, washed with brine (300 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography to give **11**.

***tert*-Butyl (*S*)-2-(4-methyloxazol-2-yl) pyrrolidine-1-carboxylate (11a)** Yield 22.1 g (60% for two steps); white solid; mp 55–57°C; R_f 0.45 [hexanes/EtOAc (1:1)]; $[\alpha]_D^{20} = -81.2$ (*c* 0.50, MeOH); MS: *m/z* 275 (MNa^+), 253 (MH^+); ^{1}H NMR ($CDCl_3$): δ 7.26 (s, 1H), 4.96 (br s, 0.35H) and 4.83 (br s, 0.65H), 3.67–3.55 (m, 1H), 3.54–3.39 (m, 1H), 2.35–2.18 (m, 1H), 2.14 (s, 3H), 2.12–1.99 (m, 2H), 1.97–1.84 (m, 1H), 1.45 (s, 3.2H) and 1.29 (s, 5.8H); ^{13}C NMR ($CDCl_3$): δ 164.4, 153.8 and 153.4, 135.9, 133.4 and 132.9, 79.3, 54.6 and 54.2, 46.4 and 46.1, 32.2 and 31.2, 28.2 and 27.9, 24.0 and 23.4, 11.3. Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.1. Found: C, 61.87; H, 8.16; N, 11.45.

***tert*-Butyl (*S*)-2-(4-isopropyloxazol-2-yl) pyrrolidine-1-carboxylate (11b)** Yield 61.4 g (70% for two steps); yellowish oil; R_f 0.41 [hexanes/EtOAc (4:1)]; $[\alpha]_D^{20} = -58.0$ (*c* 0.50, MeOH); ^{1}H NMR ($CDCl_3$): δ 7.22 (s, 1H), 4.97 (br s, 0.22H) and 4.84 (dd, J = 8.0, 4.0 Hz, 0.78H), 3.69–3.55 (m, 1H), 3.55–3.34 (m, 1H), 2.81 (sept, J = 6.7 Hz, 1H), 2.36–2.14 (m, 1H), 2.14–1.97 (m, 2H), 1.96–1.84 (m, 1H), 1.45 (s, 2.3H) and 1.28 (s, 6.7H), 1.23 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 164.2, 153.4, 146.8, 131.5 and 131.2, 79.2, 54.7 and 54.4, 46.1, 32.3 and 31.3, 28.1 and 27.9, 26.2, 24.0 and 23.4, 21.4 and 21.2. Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.27; H, 8.57; N, 10.36. MS: 281 (MH^+).

***tert*-Butyl (*S*)-2-(4-isobutyloxazol-2-yl)pyrrolidine-1-carboxylate (11c)** Yield 44.8 g (63% for two steps); yellowish oil; R_f 0.35 [hexanes/EtOAc (4:1)]; $[\alpha]_D^{20} = -60.6$ (*c* 0.50, MeOH); MS: *m/z* 295 (MH^+); ^{1}H NMR ($CDCl_3$): δ 7.25 (s, 1H), 4.95 (br s, 0.23H) and 4.83 (dd, J = 7.7, 3.6 Hz, 0.77H), 2.33 (d, J = 7.3 Hz, 2H), 2.30–2.14 (m, 1H), 2.12–1.99 (m, 2H), 1.97–1.82 (m, 2H), 1.43 (s, 2.9H) and 1.28 (s, 6.1H), 0.91 (d, J = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 164.2 and 164.0, 153.7 and 153.4, 139.35, 133.6 and 133.3, 79.21, 54.6 and 54.3, 46.3 and 46.1, 35.1, 32.3 and 31.2, 28.1 and 27.9, 27.3, 24.0 and 23.4, 22.1. Anal. Calcd for $C_{16}H_{26}N_2O_3$: C, 65.28; H, 8.90; N, 9.52. Found: C, 65.44; H, 8.56; N, 9.31.

***tert*-Butyl (*S*)-2-(4-(*tert*-butyl)oxazol-2-yl)pyrrolidine-1-carboxylate (11d)** Yield 60.7 g (72% for two steps); beige solid; mp 66–67°C; R_f 0.43 [hexanes/EtOAc (4:1)]; $[\alpha]_D^{20} = -68.4$ (*c* 0.50, MeOH); MS: *m/z* 317 (MNa^+), 295 (MH^+); ^{1}H NMR ($CDCl_3$): δ 7.20 (s, 1H), 4.97 (br s, 0.13H) and 4.85 (dd, J = 7.3, 3.6 Hz, 0.87H), 3.68–3.56 (m, 1H), 3.55–3.35 (m, 1H), 2.34–2.14 (m, 1H), 2.13–1.97 (m, 2H), 1.96–1.81 (m, 1H), 1.45 (s, 2H) and 1.27 (s, 7H), 1.24 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 164.1, 153.4, 149.9, 130.4, 79.1, 54.8 and 54.4, 46.1, 32.2 and 31.4, 30.6, 29.0, 27.9, 23.9 and 23.4. Anal. Calcd for $C_{16}H_{26}N_2O_3$: C, 65.28; H, 8.90; N, 9.52. Found: C, 65.62; H, 8.79; N, 9.24.

***tert*-Butyl (*S*)-2-(oxazol-2-yl)pyrrolidine-1-carboxylate (11e)** Yield 25.0 g (35% for two steps); yellowish oil; R_f 0.52 [hexanes/EtOAc (1:1)]; $[\alpha]_D^{20} = -54.0$ (*c* 0.50, MeOH); MS: *m/z* 261 (MNa^+), 139 ($MH^+ - C_4H_8 - CO_2$); ^{1}H NMR ($CDCl_3$): δ 7.57 (s, 1H), 7.06 (s, 1H), 5.03 (br s, 0.35H) and 4.91 (dd, *J* = 8.5, 3.5 Hz, 0.65H), 3.70–3.56 (m, 1H), 3.55–3.37 (m, 1H), 2.34–2.16 (m, 1H), 2.14–2.01 (m, 2H), 1.99–1.86 (m, 1H), 1.45 (s, 3H) and 1.28 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 164.9 and 164.6, 153.3, 137.9 and 137.5, 126.4, 79.3, 54.5 and 54.1, 46.3 and 46.0, 32.1 and 31.0, 28.1 and 27.9, 23.9 and 23.3. Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.56; H, 7.73; N, 11.76.

General procedure for synthesis of oxazoles 4a–e · 2HCl

A saturated solution of HCl in Et_2O (ca. 24% w/w, 100 mL) was precooled to 5°C and added in portions to a solution of Boc derivative **11** (0.15 mol) in dry MeOH (200 mL) at room temperature. The mixture was stirred vigorously at room temperature overnight, then concentrated (caution: violent gas emission) under reduced pressure and the residue was triturated with Et_2O (200 mL). The precipitate was filtered and washed thoroughly with MeCN (80 mL) and dried under reduced pressure to give the title product **4** · 2HCl.

(*S*)-4-Methyl-2-(pyrrolidin-2-yl)oxazole dihydrochloride (4a · 2HCl) Yield 26.5 g (77%); white solid; mp 126–128°C; $[\alpha]_D^{20} = -14.6$ (*c* 0.50, MeOH); MS: *m/z* 153 (MH^+); ^{1}H NMR (DMSO-d_6): δ 10.52 (br s, 1H, N*H*H$^+$), 9.46 (br s, 1H, NH*H*$^+$), 7.94 (q, *J* = 1.3 Hz, 1H, 5-C*H*), 4.82–4.74 (m, 1H, 2′-C*H*), 3.31–3.22 (m, 2H, 5′-CH_2), 2.40–2.30 (m, 1H, 3′-C*H*H), 2.23–2.14 (m, 1H, 3′-CH*H*), 2.11 (d, *J* = 1.3 Hz, 3H, CH_3), 2.08–1.92 (m, 2H, 4-CH_2, 1H is exchangeable with D_2O); ^{13}C NMR (DMSO-d_6): δ 158.0 (2-*C*), 136.4 (5-*C*H), 135.8 (4-*C*), 53.9 (2′-*C*H), 44.8 (5′-*C*H$_2$), 28.6 (3′-*C*H$_2$), 23.3 (4′-*C*H$_2$), 11.1 (*C*H$_3$). Anal. Calcd for $C_8H_{13}Cl_2N_2O$: C, 42.87; H, 5.85; N, 12.50; Cl, 31.64. Found: C, 42.88; H, 5.49; N, 12.15; Cl, 31.98.

(*S*)-4-Isopropyl-2-(pyrrolidin-2-yl)oxazole dihydrochloride (4b · 2HCl) Yield 43.1 g (80%); white solid; mp 134–136°C; $[\alpha]_D^{20} = -13.2$ (*c* 0.50, MeOH); MS: *m/z* 181 (MH^+); ^{1}H NMR (DMSO-d_6): δ 10.71 (br s, 1H, N*H*H$^+$), 9.49 (br s, 1H, NH*H*$^+$), 7.94 (d, *J* = 1.2 Hz, 1H, 5-C*H*), 4.82–4.71 (m, 1H, 2′-C*H*), 3.31–3.21 (m, 2H, 5′-CH_2), 2.78 (m, 1H, C*H*(CH$_3$)$_2$), 2.42–2.30 (m, 1H, 3′-C*H*H), 2.24–2.12 (m, 1H, 3′-CH*H*), 2.11–1.93 (m, 2H, 4′-CH_2), 1.18 (d, *J* = 6.9 Hz, 6H, 2CH_3); ^{13}C NMR (DMSO-d_6): δ 158.0 (2-*C*), 146.6 (4-*C*), 134.9 (5-*C*H), 54.0 (2′-*C*H), 44.9 (5′-*C*H$_2$), 28.6 (3′-*C*H$_2$), 25.7 (*C*H(CH$_3$)$_2$), 23.3 (3′-*C*H$_2$), 21.3 (2*C*H$_3$). Anal. Calcd for $C_{10}H_{18}Cl_2N_2O$: C, 47.44; H, 7.17; N, 11.07; Cl, 28.01. Found: C, 47.5; H, 6.90; N, 11.11; Cl, 28.23.

(*S*)-4-Isobutyl-2-(pyrrolidin-2-yl)oxazole dihydrochloride (4c · 2HCl) Yield 45.0 g (82%); white solid; mp 108–111°C; $[\alpha]_D^{20} = -12.4$ (*c* 0.50, MeOH); MS: *m/z* 195 (MH^+); ^{1}H NMR (DMSO-d_6): δ 10.59 (br s, 1H, N*H*H$^+$), 9.47 (br s, 1H, NH*H*$^+$), 7.95 (s, 1H, 5-C*H*), 4.84–4.74 (m, 1H, 2′-C*H*), 3.31–3.22 (m, 2H, 5′-CH_2), 2.43–2.35 (m, 1H, 3′-C*H*H), 2.34 (d, *J* = 6.9 Hz, 2H, CH_2CH(CH$_3$)$_2$), 2.24–2.12 (m, 1H, 3′-CH*H*), 2.11–1.94 (m, 2H, 4′-CH_2), 1.94–1.81 (m, 1H, CH$_2$C*H*(CH$_3$)$_2$), 0.90 (d, *J* = 6.6 Hz, 6H, 2CH_3); ^{13}C NMR (DMSO-d_6): δ 157.9 (2-*C*), 139.3 (4-*C*), 136.7 (5-*C*H), 53.9 (2′-*C*H), 44.9 (5′-*C*H$_2$), 34.4 (*C*H$_2$CH(CH$_3$)$_2$), 28.6 (3′-*C*H$_2$), 27.1 (CH$_2$*C*H(CH$_3$)$_2$), 23.3 (4′-*C*H$_2$), 22.1 (2*C*H$_3$). Anal. Calcd for $C_{11}H_{20}Cl_2N_2O$: C, 49.45; H, 7.54; N, 10.48; Cl, 26.54. Found: C, 49.13; H, 7.49; N, 10.71; Cl, 26.47.

(*S*)-4-(*tert*-Butyl)-2-(pyrrolidin-2-yl)oxazole dihydrochloride (4d · 2HCl) Yield 38.2 g (85%); white solid; mp 141–142°C (dec.); $[\alpha]_D^{20} = -13.4$ (*c* 0.50, MeOH); MS: *m/z* 195 (MH^+); ^{1}H NMR (DMSO-d_6): δ 10.70 (br s, 1H, N*H*H$^+$), 9.47 (br s, 1H, NH*H*$^+$), 7.93 (s, 1H, 5-C*H*), 4.83–4.68 (m, 1H, 2′-C*H*), 3.32–3.19 (m, 2H, 5′-CH_2), 2.42–2.30 (m, 1H, 3′-C*H*H), 2.24–2.12 (m, 1H, 3′-CH*H*), 2.10–1.90 (m, 2H, 4′-CH_2), 1.21 (s, 9H, 3CH$_3$); ^{13}C NMR (DMSO-d_6): δ 157.7 (2-*C*), 149.7 (4-*C*), 134.0 (5-*C*), 54.0 (2′-*C*H), 45.0 (5′-*C*H$_2$), 30.6 (*C*(CH$_3$)$_3$), 29.1 (3CH$_3$), 28.7 (3′-*C*H$_2$), 23.5 (4′-*C*H$_2$). Anal. Calcd for $C_{11}H_{20}Cl_2N_2O$: C, 49.45; H, 7.54; N, 10.48; Cl, 26.54. Found: C, 49.25; H, 7.44; N, 10.42; Cl, 26.77.

(*S*)-2-(Pyrrolidin-2-yl)oxazole dihydrochloride (4e · 2HCl) Yield 16.9 g (76%); beige solid; mp 167–169°C (dec.); $[\alpha]_D^{20} = -14.1$ (*c* 0.50, MeOH); MS: *m/z* 139 (MH^+); ^{1}H NMR (DMSO-d_6): δ 10.71 (br s, 1H, N*H*H$^+$), 9.59 (br s, 1H, NH*H*$^+$), 8.25 (d, *J* = 0.8 Hz, 1H, 5-C*H*), 7.32 (d, *J* = 0.8 Hz, 1H, 4-C*H*), 4.90–4.76 (m, 1H, 2′-C*H*), 3.32–3.20 (m, 2H, 5-CH_2), 2.43–2.31 (m, 1H, 3′-C*H*H), 2.22 (m, 1H, 3′-CH*H*), 2.12–1.91 (m, 2H, 4′-CH_2); ^{13}C NMR (DMSO-d_6): δ 158.4 (2-*C*), 141.1 (5-*C*H), 127.2 (4-*C*H), 53.9 (2′-*C*H), 45.0 (5′-*C*H$_2$), 28.7 (3′-*C*H$_2$), 23.4 (4′-*C*H$_2$). Anal. Calcd for $C_7H_{12}Cl_2N_2O$: C, 39.83; H, 5.73; N, 13.27; Cl, 33.59. Found: C, 39.43; H, 5.85; N, 13.36; Cl, 33.53.

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