Scalable Synthesis of *N*-Acetylated α-Amino Acid-Derived Oxazoline Ligands

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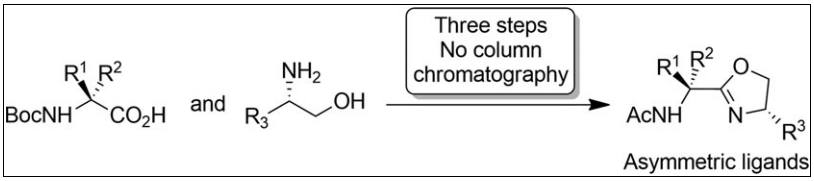

A scalable cost-effective synthesis of promising α-amino acid-derived oxazoline ligands has been developed. The advantage of the reported procedures is the use of crystallization for the purification of key intermediates and final products. The ligands obtained have recently demonstrated remarkable enantioselectivity in Pd (II) catalyzed C—H activation reactions. Hence, more rational synthetic route presented here will contribute to this rapidly growing field of chemistry.

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INTRODUCTION

Oxazoline ligands constitute a diverse family of chemical structures, which are widely used in the different types of asymmetric transformation [1–3]. Recently published papers [4,5] renewed interest to these classic molecules. Yu group specializing in C—H activation reactions introduced bidentate *N*-acetylated oxazoline-type ligands **1** (Scheme 1) prepared from α-amino acids and β-amino alcohols. Pioneering procedures for a remote enantioselective functionalization of prochiral substrates [4,5] as well as kinetic resolution [5] in the presence of palladium (II) catalysts and previously mentioned oxazolines have been developed.

Remarkable enantioselectivity achieved may stimulate further applications of this type of chiral molecules, including industrially relevant transformations [4]. Bearing in mind an emerging interest to the C—H activation chemistry and prospects of α-amino acid-derived oxazolines [6], we focused on the developing their cost-effective and scalable synthesis.

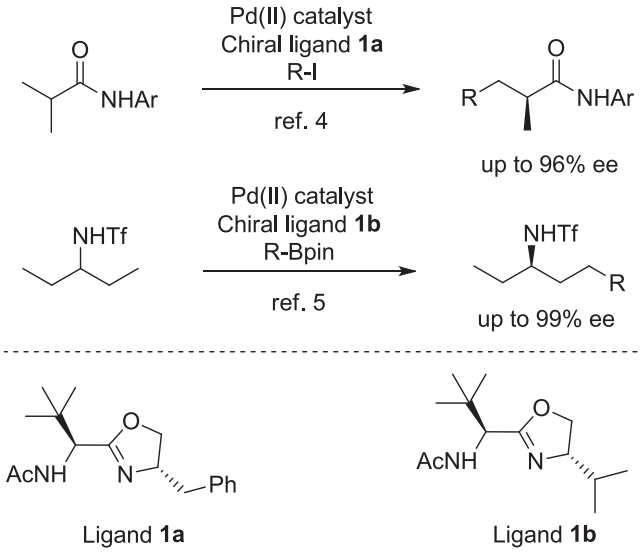
RESULTS AND DISCUSSION

We started preparation of oxazolines **1** from examining the Yu group's procedure [5]. They utilized one-step annulation method with the reagents Ph_3P and CCl_4 to convert *N*-Fmoc-protected α-amino acids directly to oxazolines (Scheme 2). Despite a sufficiently good yield, tedious chromatography was required in order to separate oxazoline from a large amount of the other reaction product triphenylphosphine oxide. In addition, careful execution of this step is necessary to prevent the side reactions [7,8]. Removal of Fmoc protecting group proceeded smoothly, while oxazoline ring was well tolerated under the reaction condition. However, this step was also followed by column chromatography due to an inevitable presence of Fmoc decomposition products.

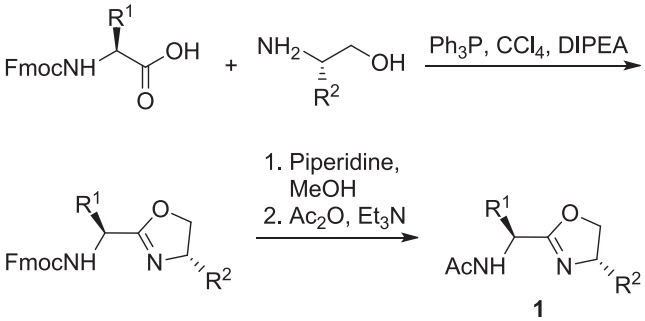
A short survey of the literature revealed that the amide coupling and the ring closure reactions could be carried out separately [9–13], and this seems to be more effective for bulk synthesis of oxazolines. We have chosen *N*-Boc-protected α-amino acids as a starting material, which is more compatible with the "atom economy" concept, given that the Boc protection should be removed prior closing an acid-sensitive oxazoline ring. Direct coupling *N*-acetyl protected α-amino acids is impossible because of a rapid racemization of the activated acid intermediate [14]. Conversely, α-amino acid derivatives **2** *N*-Boc-L-α-*tert*-butylglycine, *N*-Boc-L-valine, and *N*-Boc-D-valine were successfully coupled with near equimolar amounts of β-amino alcohols **3** L-valinol, L-phenylalaninol [11] using ethyl chloroformate as activating regent (Scheme 3).

Further, Boc-protected coupling products **4a–e** were converted into acetamides **5a–e** in a one-pot manner. Once the removal of Boc group with trifluoroacetic acid was completed, the solvent and volatile parts were simply evaporated and the residue was treated with potassium carbonate and one equivalent of acetic anhydride. Mono-acetylated products were successfully obtained [15]. Thereby, we avoided handling with highly polar and water soluble unprotected amino

Scheme 1. Examples of enantioselective C—H activation reactions in the presence of α-amino acid-derived oxazoline ligands.



Scheme 2. Synthesis of oxazolines according to Shao *et al*. [5].



alcohols. Good crystallinity of *N*-acetyl derivatives **5** was crucial for their successful separation from the impurities with close R_f. According to our observation, acetonitrile could be a solvent of choice, which allows recrystallizing **5** without a considerable yield loss. Gelation of the mixture occurred with some amides. Fortunately, this undesirable process can be suppressed by adding a small amount of water to acetonitrile or by switching a solvent.

Finally, compounds **5a–e** were treated with methanesulfonyl chloride in THF in the presence of the excess of triethylamine and catalytic amount of *p*-dimethylaminopyridine that lead to the almost pure oxazolines **1a–e**. A slightly increased temperature was required for complete conversion of less soluble amides **5a**,**c**. In most cases, final products **1** were easily purified by recrystallization from appropriate solvent or by vacuum sublimation.

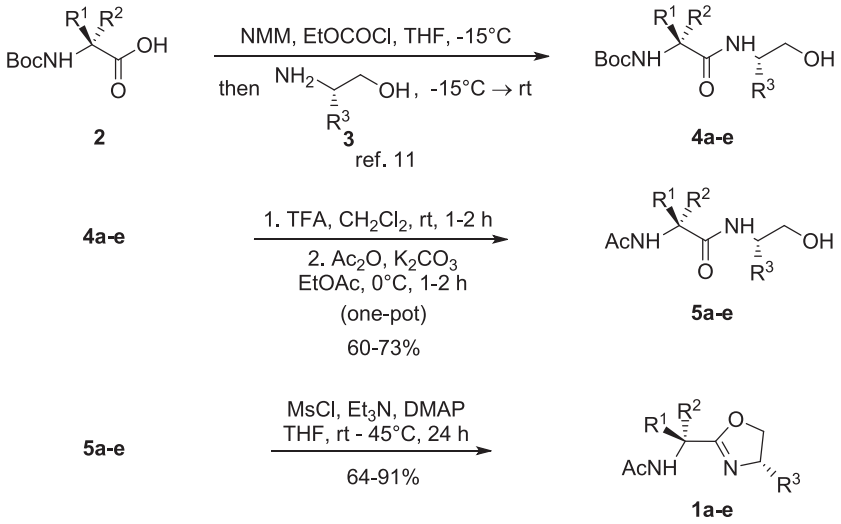
CONCLUSION

We developed a scalable three-step synthesis of promising bidentate oxazoline ligands starting from Boc-protected α-amino acids and unprotected β-amino alcohols. The advantage of this scheme is an effective use of routine crystallization for the isolation of key intermediates and final products in most cases. Rational synthetic approach can help to expand the application of these recently introduced ligands.

EXPERIMENTAL

Melting points were determined on a capillary apparatus. Optical rotations were measured with an ATAGO AP-300 polarimeter. Elemental analyses were performed using Thermo Scientific TM Flash 2000

Scheme 3. Synthesis of oxazolines.



1a, 4a, 5a: R^1 = *t*Bu, R^2 = H, R^3 = Bn; **1b, 4b, 5b**: R^1 = *t*Bu, R^2 = H, R^3 = *i*Pr;
1c, 4c, 5c: R^1 = *i*Pr, R^2 = H, R^3 = Bn; **1d, 4d, 5d**: R^1 = R^3 = *i*Pr, R^2 = H;
1e, 4e, 5e: R^1 = H, R^2 = R^3 = *i*Pr; **2**: R^1 = *t*Bu, R^2 = H (*N*-Boc-L-α-tert-butylglycine);
2: R^1 = *i*Pr, R^2 = H (*N*-Boc-L-valine); **2**: R^1 = H, R^2 = *i*Pr (*N*-Boc-D-valine);
3: R^3 = *i*Pr (L-valinol); **3**: R^3 = Bn (L-phenylalaninol).

CHNS/O analyzer. IR spectra were recorded on a Vertex 70 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, on a Bruker Avance 500 spectrometer in solvent DMSO-d_6. Chemical shifts were referred to the signals of the residual DMSO (δ = 2.50 ppm in ^{1}H NMR and δ = 39.52 ppm in ^{13}C NMR). TLC analysis was performed on Silica gel 60 F 254 plates; column chromatography was performed on silica gel 70–230 mesh. β-Amino alcohols and Boc-protected α-amino acids were purchased from Chem-Impex Intl. Tetrahydrofuran and triethylamine were freshly distilled from sodium, dichloromethane was distilled from calcium hydride, and ethyl acetate was dried with calcium chloride and distilled.

Synthesis of compounds 4a–e. Compounds **4a–e** were prepared by coupling Boc-protected α-amino acids **2** with β-amino alcohols **3** in accordance with common procedure [11], except that isopropyl chloroformate was replaced with ethyl chloroformate. For compound **4a**, reported procedure [11] was slightly modified (see succeeding texts). Compounds **4b** and **4c** were used without purification.

tert-Butyl[(1S)-1-{[(1S)-1-benzyl-2-hydroxyethyl]carbamoyl}-2,2-dimethylpropyl]carbamate (4a). A vigorously stirred solution of Boc-L-α-*tert*-butylglycine (12.15 g, 52.5 mmol) in THF (150 mL) was cold in an ice-salt bath to the temperature −15°C. *N*-Methylmorpholine (5.66 g, 56.0 mmol) and ethyl chloroformate (5.79 g, 53.3 mmol) were added subsequently *via* syringe, and the stirring was continued for 30 min, whereupon a solution of L-phenylalaninol (8.24 g, 54.5 mmol) in THF (60 mL) was added dropwise to the reaction. The mixture was additionally stirred for 2 h, the cooling bath was removed, and the solvent was evaporated in vacuo. Ethyl acetate (300 mL) and the saturated solution of NH_4Cl (300 mL) were added to the residue, and the biphasic mixture was heated with stirring until all solids were dissolved. Organic and aqueous layers were separated, and the aqueous layer was additionally extracted with warm ethyl acetate (2 × 150 mL). Combined organic extracts were washed with 40% aqueous solution of K_2CO_3 (100 mL), dried with Na_2SO_4, and evaporated under reduced pressure. The residue was recrystallized from acetonitrile giving pure amide **4a** as colorless crystals, yield 14.0 g (73%), mp 200–205°C; $[\alpha]_D^{20} = -59.5$ (*c* = 1.2 in MeOH); IR (KBr): 3334, 3253, 1680, 1633, 1562 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.73 (d, 1H, NH, *J* = 8.3 Hz,), 7.26–7.12 (m, 5H, Ph), 6.29 (d, 1H, NHBoc, *J* = 9.7 Hz), 4.78 (app. t, 1H, OH, *J* = 5.3 Hz), 4.01–3.86 (m, 1H, $CHCH_2OH$), 3.79 (d, 1H, CHtBu, *J* = 9.7 Hz), 3.36–3.32 (m, 1H, CH_2OH), 3.30–3.23 (m, 1H, CH_2OH), 2.86 (dd, 1H, CH_2Ph, *J* = 13.8, 5.4 Hz), 2.61 (dd, 1H, CH_2Ph, *J* = 13.8, 8.6 Hz,), 1.38 (s, 9H, O*t*Bu), 0.82 (s, 9H, *t*Bu); ^{13}C NMR (DMSO-d_6): δ 169.8 (C), 155.2 (C), 139.1 (C), 129.1 (2CH), 128.0 (2CH), 125.9 (CH), 78.0 (C), 62.6 (CH), 62.0 (CH_2),

52.2 (CH), 36.3 (CH_2), 33.9 (C), 28.2 ($3CH_3$), 26.6 ($3CH_3$). *Anal*. Calcd for $C_{20}H_{32}N_2O_4$: C, 65.91; H, 8.85. Found: C, 66.05; H, 8.96.

General procedure for compounds 5a–e. Trifluoroacetic acid (40 mL) was added to a stirred and ice-cooled solution of Boc-protected derivative **4** (38.0 mmol) in CH_2Cl_2 (350 mL). The ice bath was removed, and the stirring was continued at room temperature for 2 h after which the solvent was evaporated in vacuo. The resulting residue was dissolved in ethyl acetate (380 mL), and anhydrous powdered K_2CO_3 (27.6 g, 200 mmol) was added portionwise. The mixture was placed in the ice bath, and a solution of acetic anhydride (3.88 g, 38.0 mmoL) in ethyl acetate (30 mL) was added dropwise to the vigorously stirred mixture. The stirring was continued for 1 h in the ice bath and for 15 min at room temperature, and then brine (500 mL) was added. Two-phase mixture was heated to prevent crystallization of the product and quickly transferred to the separatory funnel. The layers were separated, and the aqueous layer was extracted with ethyl acetate (5 × 100 mL). Combined organic phases were dried over Na_2SO_4 for several minutes, filtrated, and evaporated in vacuo. The residue was recrystallized from an appropriate solvent to afford pure acetyl derivatives **5**.

The yields of **5a**,**d**,**e** are given to 38.0 mmol of starting material **4a**,**d**,**e**; the yields of **5b** and **5c** are given to 38.0 mmol of *N*-Boc-L-α-*tert*-butylglycine and *N*-Boc-L-valine.

(2S)-2-(Acetylamino)-N-[(1S)-1-benzyl-2-hydroxyethyl]-3,3-dimethylbutanamide (5a). Recrystallized from *tert*-butyl methyl ether as colorless crystals, yield 6.93 g (60%), mp 116–120°C; $[\alpha]_D^{20} = -56.9$ (c = 1.3 in MeOH); IR (KBr): 3327, 1662, 1633, 1566, 1518 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.84 (d, 1H, NH, J = 8.4 Hz), 7.72 (d, 1H, NHAc, J = 9.7 Hz), 7.25–7.11 (m, 5H, Ph), 4.74 (app. t, 1H, OH, J = 5.5 Hz), 4.20 (d, 1H, CHtBu, J = 9.7 Hz), 3.96–3.86 (m, 1H, $CHCH_2OH$), 3.34 (dt, 1H, CH_2OH, J = 10.5, 5.3 Hz), 3.26 (dt, 1H, CH_2OH, J = 10.5, 6.0 Hz), 2.87 (dd, 1H, CH_2Ph, J = 13.7, 5.3 Hz), 2.57 (dd, 1H, CH_2Ph, J = 13.7, 8.6 Hz), 1.85 (s, 3H, CH_3CO), 0.86 (s, 9H, *t*Bu); ^{13}C NMR (DMSO-d_6): δ 169.7 (C), 168.9 (C), 139.1 (C), 129.1 (2CH), 128.0 (2CH), 125.8 (CH), 62.6 (CH_2), 59.7 (CH), 52.2 (CH), 36.4 (CH_2), 33.9 (C), 26.7 ($3CH_3$), 22.5 (CH_3). *Anal*. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H 8.55. Found: C, 66.50; H, 8.58.

(2S)-2-(Acetylamino)-N-[(1S)-1-(hydroxymethyl)-2-methylpropyl]-3,3-dimethylbutanamide (5b). Recrystallized from acetonitrile as colorless crystals, yield 7.00 g (71%), mp 176–179°C; $[\alpha]_D^{20} = -48.8$ (c = 0.9 in MeOH); IR (KBr): 3380, 3287, 1632, 1564, 1544 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.77 (d, 1H, NHAc, J = 9.5 Hz), 7.54 (d, 1H, NH, J = 9.0 Hz), 4.46 (app. t, 1H, OH, J = 5.3 Hz), 4.27 (d, 1H, CHNHAc, J = 9.5 Hz), 3.62–3.57 (m, 1H, $CHCH_2OH$), 3.35–3.32 (m, 2H, CH_2OH), 1.87 (s, 3H, CH_3CO), 1.84–1.75 (m, 1H, $CHMe_2$), 0.90 (s, 9H, *t*Bu, J = 7.6 Hz), 0.82 (d, 3H, $CHMe_2$, J = 6.8 Hz), 0.80 (d, 3H, $CHMe_2$, J = 6.8 Hz); ^{13}C NMR (DMSO-d_6): δ 170.1 (C), 169.0 (C), 61.4 (CH_2), 59.8 (CH), 55.4 (CH), 34.0 (C), 28.1 (CH), 26.8 ($3CH_3$), 22.5 (CH_3), 19.6 (CH_3), 17.9 (CH_3). *Anal*. Calcd for $C_{13}H_{26}N_2O_3$: C, 60.44; H, 10.14. Found: C, 60.58; H, 10.10.

(2S)-2-(Acetylamino)-N-[(1S)-1-benzyl-2-hydroxyethyl]-3-methylbutanamide (5c). Recrystallized from acetonitrile containing 5% of water as colorless crystals, yield: 7.18 g (65%), mp 187–191°C; $[\alpha]_D^{20} = -55.1$ (c = 1.3 in MeOH); IR (KBr): 3335, 1661, 1632, 1565, 1521 cm^{-1}; ^1H NMR (500 MHz): δ 7.79 (d, 1H, NHAc, J = 9.0 Hz), 7.76 (d, 1H, NH, J = 8.4 Hz), 7.26–7.14 (m, 5H, Ph), 4.76 (app. t, 1H, OH, J = 5.3 Hz), 4.08 (dd, 1H, CHiPr, J = 9.0, 7.3 Hz), 3.97–3.82 (m, 1H, $CHCH_2OH$), 3.36–3.31 (m, 1H, CH_2OH), 3.29–3.21 (m, 1H, CH_2OH), 2.86 (dd, 1H, CH_2Ph, J = 13.7, 5.4 Hz), 2.60 (dd, 1H, CH_2Ph, J = 13.7, 8.5 Hz), 1.90–1.85 (m, 1H, $CHMe_2$), 1.84 (s, 3H, CH_3CO), 0.80–0.76 (m, 6H, $CHMe_2$); ^{13}C NMR (DMSO-d_6): δ 170.7 (C), 169.1 (C), 139.1 (C), 129.2 (2CH), 128.1 (2CH), 125.9 (CH), 62.5 (CH_2), 57.8 (CH), 52.3 (CH), 36.4 (CH_2), 30.4 (CH), 22.5 (CH_3), 19.2 (CH_3), 18.2 (CH_3). *Anal*. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27. Found: C, 65.55; H, 8.26.

(2S)-2-(Acetylamino)-N-[(1S)-1-(hydroxymethyl)-2-methylpropyl]-3-methylbutanamide (5d). Recrystallized from acetonitrile as colorless crystals, yield 6.48 g (70%), mp 192–196°C; $[\alpha]_D^{20} = -43.5$ (c = 1.0 in MeOH); IR (KBr): 3383, 3294, 1629, 1566, 1547 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.86 (d, J = 8.9 Hz, 1H, NHAc), 7.47 (d, J = 9.1 Hz, 1H, NH), 4.49 (app. t, 1H, OH, J = 5.3 Hz), 4.13 (dd, 1H, CHNHAc, J = 8.9, 7.4 Hz), 3.63–3.51 (m, 1H, $CHCH_2OH$), 3.39–3.30 (m, 2H, CH_2OH), 1.97–1.89 (m, 1H, $CHMe_2$), 1.85 (s, 3H, CH_3CO), 1.83–1.77 (m, 1H, $CHMe_2$), 0.85–0.81 (m, 9H, $2CHMe_2$), 0.80 (d, 3H, $CHMe_2$, J = 6.8 Hz); ^{13}C NMR (DMSO-d_6): δ 171.0 (C), 169.1 (C), 61.4 (CH_2), 58.0 (CH), 55.4 (CH), 30.3 (CH), 28.1 (CH), 22.5 (CH_3), 19.6 (CH_3), 19.3 (CH_3), 18.4 (CH_3), 18.0 (CH_3); *Anal*. Calcd for $C_{12}H_{24}N_2O_3$: C, 58.99; H 9.90. Found: C, 58.80; H, 9.90.

(2R)-2-(Acetylamino)-N-[(1S)-1-(hydroxymethyl)-2-methylpropyl]-3-methylbutanamide (5e). Recrystallized from acetonitrile as colorless crystals, yield 6.78 g (73%), mp 220–225°C; $[\alpha]_D^{20} = +6.5$ (c = 0.3 in MeOH); IR (KBr): 3380, 3288, 1627, 1566, 1549 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.85–7.77 (d, 1H, NH, J = 8.9 Hz), 7.63 (d, 1H, NH, J = 8.9 Hz), 4.50 (app. t, 1H, OH, J = 5.4 Hz), 4.22 (dd, 1H, CHNHAc, J = 8.9, 6.6 Hz), 3.60–3.53 (m, 1H, $CHCH_2OH$), 3.37–3.34 (m, 2H, CH_2OH), 1.97–1.88 (m, 1H, $CHMe_2$), 1.86 (s, 3H, CH_3CO), 1.85–1.78 (m, 1H, $CHMe_2$), 0.85–0.80 (m, 12H, $2CHMe_2$); ^{13}C NMR (DMSO-d_6): δ 171.0 (C),

169.2 (C), 61.2 (CH_2), 57.8 (CH), 55.6 (CH), 30.8 (CH), 27.9 (CH), 22.5 (CH_3), 19.7 (CH_3), 19.4 (CH_3), 18.1 (CH_3), 18.0 (CH_3). *Anal*. Calcd for $C_{12}H_{24}N_2O_3$: C, 58.99; H 9.90. Found: C, 58.92; H, 9.88.

General procedure for oxazolines 1a–e. Triethylamine (13.9 mL, 100 mmol) and *p*-(dimethylamino) pyridine (245 mg, 2.0 mmol) were added to a stirred suspension (or solution) of compound **5** (22.0 mmol) in THF (150 mL). The mixture was cold in an ice bath, and methanesulfonyl chloride (3.44 g, 30.0 mmol) in 10 mL of THF was added dropwise. The cooling bath was removed, and the mixture was allowed to stir at room temperature (in the case of starting materials **5b**,**d**,**e**) or at 45°C (in the case of starting materials **5a**,**c**) for 24 h. The progress of the reaction was monitored by TLC (eluent CH_2Cl_2–MeOH, 15:1, two runs). Once the reaction was completed, the solvent was evaporated in vacuo, and saturated solution of NH_4Cl_4 (150 mL) was added to the residue. The product was extracted with ethyl acetate (5 × 100 mL); combined organic phases were washed with 50% K_2CO_3 solution, dried over Na_2SO_4. The solvent was evaporated in vacuo to give products 1, which were purified as indicated in the following.

The yields are given to 22.0 mmol of starting material **5a–e**.

N-{(1S)-1-[(4S)-4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl]-2,2-dimethylpropyl}acetamide (1a). Recrystallized from CCl_4 as colorless crystals, yield 5.58 g (88%), mp 128–130°C; $[\alpha]_D^{20}$ = −86.1 (*c* = 1.2 in MeOH); IR (KBr): 3302, 1659, 1608, 1531, 1510 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.02 (d, 1H, NH, *J* = 9.7 Hz), 7.30–7.17 (m, 5H, Ph), 4.40 (d, 1H, CHNH, *J* = 9.7 Hz), 4.35–4.29 (m, 1H, CH-N=C), 4.18 (dd, 1H, CH_2O, *J* = 8.9, 8.5 Hz), 3.92 (dd, 1H, CH_2O, *J* = 8.5, 7.2 Hz), 2.84 (dd, 1H, CH_2Ph, *J* = 13.6, 6.4 Hz), 2.67 (dd, 1H, CH_2Ph, *J* = 13.6, 7.3 Hz), 1.90 (s, 3H, CH_3CO), 0.92 (s, 9H, *t*Bu); ^{13}C NMR (DMSO-d_6): δ 169.0 (C), 165.0 (C), 138.2 (C), 129.3 (2CH), 128.2 (2CH), 126.1 (CH), 70.9 (CH_2), 66.5 (CH), 54.7 (CH), 41.2 (CH_2), 34.2 (C), 26.6 ($3CH_3$), 22.4 (CH_3). *Anal*. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39. Found: C, 70.93; H, 8.38.

N-{(1S)-2,2-Dimethyl-1-[(4S)-4-(1-methylethyl)-4,5-dihydro-1,3-oxazol-2-yl]propyl}acetamide (1b). Sublimated in vacuo, yield 4.44 g (84%), colorless crystals, mp 65–66°C; $[\alpha]_D^{20}$ = −120.0 (*c* = 1.4 in MeOH); IR (KBr): 3315, 3066, 1684, 1566, 1632 cm^{-1}; ^1H and ^{13}C NMR spectra were similar to reported [5].

N-{(1S)-1-[(4S)-4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl]-2-methylpropyl}acetamide (1c). Recrystallized from CCl_4 as colorless crystals, yield 5.06 g (84%), mp 111–115°C; $[\alpha]_D^{20}$ = −86.1 (*c* = 1.2 in MeOH); IR (KBr): 3315, 1660, 1606, 1533 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.07 (d, 1H, NH, *J* = 9.6 Hz), 7.30–7.17 (m, 5H, Ph), 4.38–4.27 (m, 2H, CHNH, CH-N=C), 4.21 (dd, 1H, CH_2O, *J* = 9.2, 8.3 Hz), 3.92 (dd, 1H, CH_2O, *J* = 8.3, 7.3 Hz), 2.83 (dd, 1H, CH_2Ph, *J* = 13.6, 6.4 Hz), 2.66 (dd, 1H, CH_2Ph, *J* = 13.6, 7.2 Hz), 1.98–1.89 (m, 1H, $CHMe_2$), 1.87 (s, 3H, CH_3CO), 0.85 (d, 3H, $CHMe_2$, *J* = 6.8 Hz), 0.84 (d, 3H, $CHMe_2$, *J* = 6.8 Hz); ^{13}C NMR (DMSO-d_6): δ 169.1 (C), 165.5 (C), 138.2 (C), 129.3 (2CH), 128.2 (2CH), 126.1 (CH), 71.3 (CH_2), 66.5 (CH), 52.0 (CH), 41.2 (CH_2), 30.5 (CH), 22.4 (CH_3), 19.1 (CH_3), 18.3 (CH_3). *Anal*. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08. Found: C, 70.15; H, 8.10.

N-{(1S)-2-Methyl-1-[(4S)-4-(1-methylethyl)-4,5-dihydro-1,3-oxazol-2-yl]propyl}acetamide (1d). Purified by column chromatography with a mixture of CH_2Cl_2 and MeOH (50:1–20:1) as eluent, yield: 4.55 g (91%), viscous liquid; $[\alpha]_D^{20}$ = −87.5 (*c* = 1.3 in MeOH); IR (KBr): 3365, 3222, 1653, 1550 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.06 (d, *J* = 9.1 Hz, 1H, NH), 4.37–4.28 (m, 1H, CHNH), 4.22 (app. t, 1H, CH_2O, *J* = 9.0 Hz), 3.93 (app. t, 1H, CH_2O, *J* = 8.3 Hz), 3.85–3.78 (m, 1H, CH-N=C), 1.97–1.92 (m, $CHMe_2$), 1.85 (s, 3H, CH_3CO), 1.63–1.59 (m, 1H, $CHMe_2$), 0.90–0.83 (m, 9H, $2CHMe_2$), 0.81 (d, *J* = 6.7 Hz, 3H, $CHMe_2$); ^{13}C NMR (DMSO-d_6): δ 169.1 (C), 165.1 (C), 71.2 (CH), 69.5 (CH_2), 52.1 (CH), 32.1 (CH), 30.5 (CH), 22.4 (CH_3), 19.1 (CH_3), 18.6 (CH_3), 18.3 (CH_3), 18.2 (CH_3). *Anal*. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.68; H, 9.80. Found: C, 63.50; H, 9.86.

N-{(1R)-2-Methyl-1-[(4S)-4-(1-methylethyl)-4,5-dihydro-1,3-oxazol-2-yl]propyl}acetamide (1e). Recrystallized from acetonitrile as colorless crystals, yield 2.59 g (52%), concentration of the mother liquor gave additionally 0.60 g (12%) of crystals, mp 116–120°C; $[\alpha]_D^{20}$ = +15.0 (*c* = 1,0 in MeOH); IR (KBr): 3381, 3234, 3201, 1655, 1552 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.05 (d, 1H, NH, *J* = 9.4 Hz), 4.35–4.29 (m, 1H, CHNH), 4.23 (dd, 1H, CH_2O, *J* = 9.2, 8.3 Hz), 3.90 (dd, 1H, CH_2O, *J* = 8.3, 8,0 Hz), 3.87–3.82 (m, 1H, CH-N=C), 1.97–1.92 (m, 1H, $CHMe_2$), 1.85 (s, 3H, CH_3CO), 1.67–1.62 (m, 1H, $CHMe_2$), 0.88–0.84 (m, 9H, $2CHMe_2$), 0.82 (d, 3H, $CHMe_2$, *J* = 6.8 Hz); ^{13}C NMR (DMSO-d_6): δ 169.0 (C), 165.3 (C), 71.2 (CH), 69.3 (CH_2), 51.9 (CH), 31.9 (CH), 30.5 (CH), 22.4 (C), 19.1 (CH_3), 18.6 (CH_3), 18.3 (CH_3), 18.1 (CH_3). *Anal*. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.68, H, 9.80. Found: C, 63.52; H, 9.80.

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