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Acid catalyzed monodehydro-2,5-diketopiperazine formation from *N*-α-ketoacyl amino acid amides

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ABSTRACT

We have developed a new synthetic method for monodehydro-2,5-diketopiperazines (monodehydroDKPs), which is based on an acid catalyzed cyclization of *N*-α-ketoacyl amino acid amides. Using this cyclization reaction, monodehydroDKP was formed with no or slight racemization in case that *N*-α-ketoacyl amino acid amides with β-aliphatic-α-ketoacyl groups and sterically unhindered *N*-substituting groups at the C-terminal amide nitrogen were used in the presence of catalytic amount of *p*-TsOH (3–5 mol %) or 10% TFA. In the case of β-aryl-α-ketoacyl amino acid derivatives, in which an enol form predominantly exists by conjugation with the aromatic ring, racemization could be minimized by optimizing the reaction conditions (5 mol % *p*-TsOH, reflux for 6 h), although the chemical yield could not be dramatically improved. However, this reaction condition was successfully applied to the synthesis of a tubulin depolymerization agent, (−)-*tert*-butyl-oxa-phenylahistin, with no racemization.

1. Introduction

Monodehydro-2,5-diketopiperazine (monodehydroDKP, **1**) is a cyclic dipeptide with a dehydrated structure on one side of the ring. Many naturally occurring derivatives of the monodehydroDKP possessing varied biological activity have been discovered such as phenylahistin with microtubule depolymerization activity,[1] *cyclo* (dehydroAla-L-Leu) with α-glucosidase inhibitory activity,[2] barettin with selective 5HT-ligand activity,[3] neoechinulin A with cytoprotection activity,[4] cristatin A with immunosuppressive activity,[5] and golmaenone with radical scavenging activity,[6] etc. Among these compounds, phenylahistin was recognized as a new lead compound for anticancer agents. Recently, we developed a phenylahistin derivative NPI-2358 with highly potent cytotoxic and vascular disrupting activities and this compound is currently in the Phase I clinical trials for anticancer drug in the US as a vascular disrupting agent (VDA)[7] that would afford an important contribution in the future cancer therapy (Fig. 1). Additionally, monodehydroDKPs are useful building blocks and templates for combinatorial chemistry.

In the synthesis of monodehydroDKPs, racemization at the α-position of α-amino acids is often observed during base catalyzed cyclization of the corresponding dipeptide units, or during base catalyzed introduction of the dehydro-moiety onto the DKP ring with a chiral side chain at the opposite α-position (Fig. 1, compound **1**).[8] In order to develop a new method that reduces such unfavorable racemization and to provide a new efficient synthetic route of monodehydroDKPs, we focused our work on Gladiali et al.'s report that the reaction of α-ketoester and Boc-NH_2 in the presence of a catalytic amount of *p*-TsOH resulted in the formation of dehydroamino acid as shown in Scheme 1A.[9] It was thought that, if this acid catalyzed reaction was applied to an intramolecular reaction, monodehydroDKPs would be formed with no racemization (Scheme 1B). Hence, we applied Gladiali's method to corresponding precursors of monodehydroDKPs, i.e., *N*-α-ketoacyl amino acid amides. Here, we describe a new method based on an acid catalyzed cyclization of *N*-α-ketoacyl amino acid amides to facilitate the synthesis of monodehydroDKPs. The limitation of this method in the use of *N*-β-aryl-α-ketoacyl amino acid amides was also discussed.

2. Results and discussion

2.1. Acid catalyzed monodehydroDKP formation

To examine the acid catalyzed formations of monodehydroDKPs **4** from α-ketoacyl amino acid amides **3**, a series of **3** as starting materials were firstly prepared by the coupling between α-ketocarboxylic acid **1** and amino acid amides **2** using an EDC–HOBt method. As Table 1 shows, although the chemical yields of **3** were moderate, the obtained **3** was refluxed in

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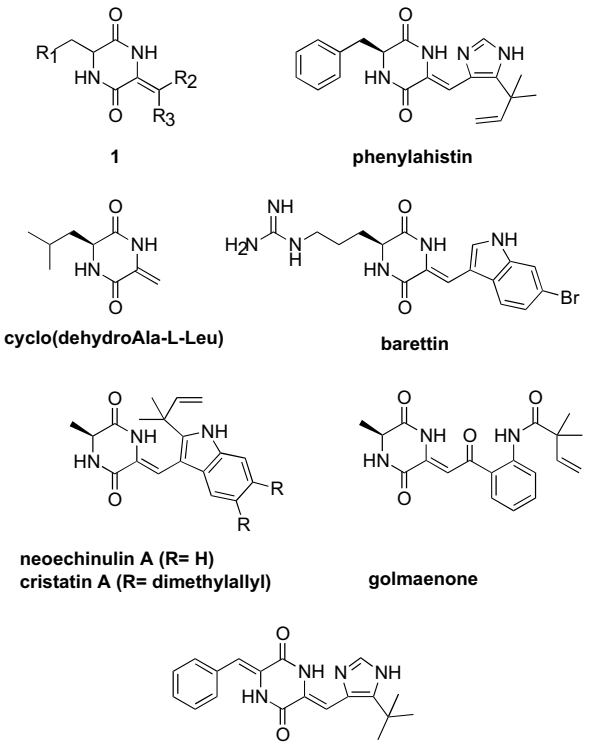
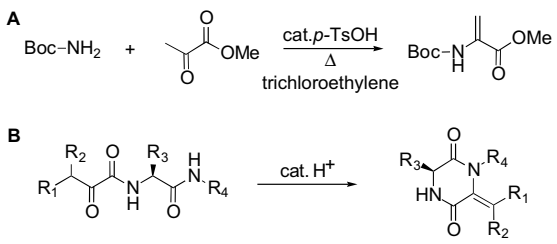


Figure 1. Chemical structures of naturally occurring monodehydroDKPs and DKP anticancer agent NPI-2358.



Scheme 1. (A) Gladiali's method for the synthesis of dehydroamino acid derivatives. (B) A new synthetic strategy of monodehydroDKP based on A.

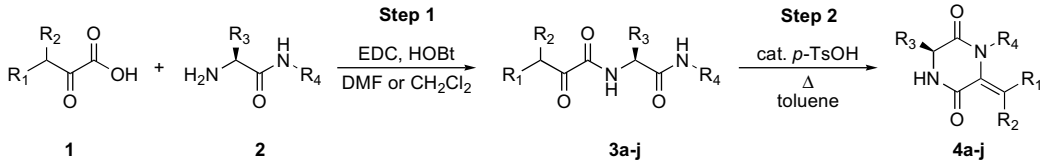
toluene in the presence of a catalytic amount of *p*-TsOH (3–5 mol %). Enantiomeric excess of the product was determined by chiral HPLC using a CHIRALCEL OD column eluted with *n*-hexane/ethanol (5:1). As shown in entries a–c (Table 1), the acid catalyzed cyclization of pyruvoyl- or β-aliphatic-α-ketoacyl-Phe-NH_2 was successfully proceeded to give corresponding monodehydroDKPs with a good chemical yield. During reaction no racemization was observed in these compounds. Therefore, an idea of monodehydroDKPs formation via acid catalyzed intramolecular cyclization based on Gladiali's method was realized. However, when *N*-phenylpyruvoyl derivative (entry d in Table 1) was used as a substrate, this substrate remained after 18 h reflux, the chemical yield of desired product was lowered, and partial racemization was observed. This low reactivity, resulting in the racemization, will be discussed in Sections 2.3 and 2.5. In entries b and d (Table 1), energetically favored *Z*-configuration was selectively obtained.

Next, we examined the effect of an alkyl-substitution on the C-terminal amide nitrogen in **3e–h** (entries e–h in Table 1). In spite of the electron donating effect of the alkyl groups, the chemical yields of the corresponding monodehydroDKPs were lowered except for the allyl group (entry h, 92% yield), but no racemization was observed. Since the derivative with a bulky isopropyl group showed the lowest yield (entry f, 20% yield), the steric factor seemed to be more influenced than the electron donating effect of the alkyl group in this cyclization reaction. Therefore, unhindered groups such as an allyl group can favorably be inserted at this position for obtaining molecular diversity in the future combinatorial synthesis.

Furthermore, fixing the substituting group on the C-terminal amide nitrogen to the allyl group, monodehydroDKPs with L-Leu and L-Ser(Bzl) were also synthesized in place of the L-Phe residue (entries i and j in Table 1). Similar chemical yield to the L-Phe derivative was obtained in the case of L-Leu derivative, while L-Ser(Bzl) derivative needed longer reaction time and showed moderate chemical yield probably due to some steric effect. No racemization was observed in both cases.

As a comparative study, HCl·H-L-Phe-ΔAla-OMe was refluxed in methanol in the presence of triethylamine (2.5 equiv) for 12 h. Racemization (93% ee) at the α-position of the Phe residue was observed (see Supplementary data).

Table 1
Synthesis of monodehydroDKPs by acid catalyzed cyclization of *N*-α-ketoacyl amino acid amides



Entry	R_1	R_2	R_3	R_4	Yield (%), step 1	*p*-TsOH (mol %)	Time (h)	Yield (%), step 2	*E*/*Z*[a]	ee (%)[b]
a	H	H	Bzl	H	65	5	18	96	—	>99[c]
b	Me	H	Bzl	H	94	5	17	86	1/25	>99[c]
c	Me	Me	Bzl	H	74	5	18	94	—	>99[c]
d	Ph	H	Bzl	H	66	5	18	35	1/>99[d]	74
e	H	H	Bzl	Bn	64	3	24	53	—	>99[c]
f	H	H	Bzl	*i*-Pr	73	5	72	20	—	>99[c]
g	H	H	Bzl	*i*-Bu	57	3	72	43	—	>99[c]
h	H	H	Bzl	Allyl	40	3	20	92	—	>99[c]
i	H	H	*i*-Bu	Allyl	63	5	10	96	—	>99[c]
j	H	H	CH_2-O-Bzl	Allyl	86	5	40	69	—	>99[c]

[a] *E*/*Z* ratio was determined by NMR.
[b] Enantiomeric excess values were determined by chiral HPLC using CHIRALCEL OD column eluted with *n*-hexane/ethanol (5:1).
[c] No another enantiomer was detected.
[d] The *E*-form was not detected.

2.2. Effect of acids on the cyclization reaction

To understand the effect of acids, which were required in the cyclization reaction, a model substrate pyruvoyl-Phe-NH-allyl **3h** was refluxed in the presence of a variety of acids. As shown in Table 2, the reaction did not proceed with a catalytic amount (3 mol %) of TFA (pK_a=−0.25) or MSA (pK_a=−2.6). However, in the catalytic use of stronger acids *p*-TsOH (pK_a=−6.57) and TFMSA (pK_a=−14), monodehydroDKP **4h** was produced with no racemization. Especially, the use of *p*-TsOH resulted in the highest chemical yield (92%) of desired product. Alternatively, the effect of the large amount of TFA or AcOH as a weaker acid was evaluated. TFA solution (1%) (corresponding to 50 mol %) in toluene, promoted the production of **4h** in 26% yield and a higher chemical yield of 62% was obtained in 10% TFA. AcOH (10%, pK_a=4.76) was not effective in this cyclization reaction. As a result, the catalytic use of *p*-TsOH with a pK_a value of −6.57 was suitable for this cyclization reaction.

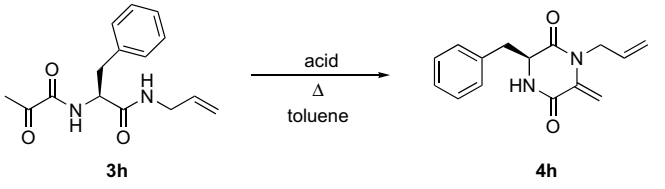
2.3. MonodehydroDKP formation from a β-aryl-α-keto acid derivative

To improve the observed low reactivity of *N*-phenylpyruvoyl derivative **3d** (entry d in Table 1 or entry 4 in Table 3), optimization of the reaction conditions was conducted. As Table 3 shows, by increasing the amount of *p*-TsOH or reaction time, racemization at the α-position of the Phe residue was increased and the chemical yield was not well improved, suggesting that a longer exposure to the acid might enhance racemization at the non-reactive site in the monodehydroDKP formation. The best reaction condition obtained among these experiments was 5 mol % *p*-TsOH and 6 h reflux, resulted in desired **4d** in 34% yield with no racemization (entry 3 in Table 3). The results also suggested that the use of 1 mol % *p*-TsOH could induce no racemization even in a longer time reaction (entries 1 and 2 in Table 3).

2.4. Application: synthesis of *tert*-butyl-oxa-phenylahistin

As one of the chiral monodehydroDKPs, we focused on *tert*-butyl-oxa-phenylahistin **11**, a derivative of natural microtubule depolymerization agent, phenylahistin,[1] and synthesized this compound by using acid catalyzed intramolecular cyclization of the corresponding β-aryl-α-ketoacyl amino acid derivative as a key step. To obtain this key amino acid intermediate, as shown in Scheme 2, we first synthesized *N*-*tert*-butoxycarbonyl-α-dimethylphosphonoglycine-*tert*-butyl ester **6** from *tert*-butyl-*P*,*P*-dimethylphosphonoacetate **5** in two steps by using the known procedure.[11,12] Briefly, compound **5** was diazotized with tosyl azide (TsN_3) in the presence of NaH, and then the obtained diazo compound was refluxed with Boc–NH_2 in the presence of $Rh_2(OAc)_4$ catalyst in toluene to give desired **6** (51% yield in two steps). *tert*-Butyl-1-(*tert*-butoxycarbonyl)-2-(5-*tert*-butyloxazol-4-yl)vinylcarbamate **8** was then synthesized from compound **6** by Horner–Emmons reaction with 5-*tert*-butyl-4-oxazolecarboxaldehyde **7**, which were prepared from ethyl isocyanoacetate in three steps.[13] In this reaction, only *Z* isomer was obtained from the NMR analysis.[14] Then, compound **8** was treated with 4 M HCl/

Table 2
Effect of acids on cyclization reaction

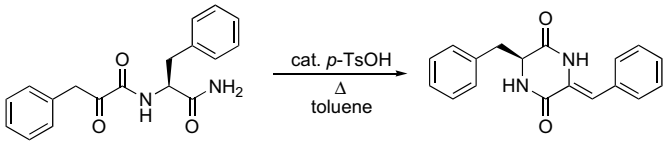


3h **4h**

Entry	Acid	Amount	pK_a[a]	Time (h)	Yield (%)	ee (%)[b]
1	TFA	3 mol %	−0.25	24	N.D. (0.3)[e]	N.D.
2	MSA	3 mol %	−2.6	24	N.D. (1)[e]	N.D.
3	*p*-TsOH	3 mol %	−6.57	20	92	>99[c]
4	TFMSA	3 mol %	−14	24	41 (85)[e,f]	>99[c]
5	TFA	0.5%[d]	−0.25	24	N.D. (1)[e]	N.D.
6	TFA	1%[d]	−0.25	24	26 (47)[e]	>99[c]
7	TFA	5%[d]	−0.25	24	42 (76)[e]	>99[c]
8	TFA	10%[d]	−0.25	24	62 (85)[e]	>99[c]
9	AcOH	10%[d]	4.76	24	N.D. (7)[e]	N.D.

[a] See Ref. 10.
[b] Enantiomeric excess values were determined by chiral HPLC using CHIRALCEL OD column eluted with *n*-hexane/ethanol (5:1).
[c] No another enantiomer was detected.
[d] v/v % in toluene.
[e] The values in the parenthesis indicate HPLC yield. N.D.: not determined.
[f] The chemical yield decreased due to the existence of inseparable impurity.

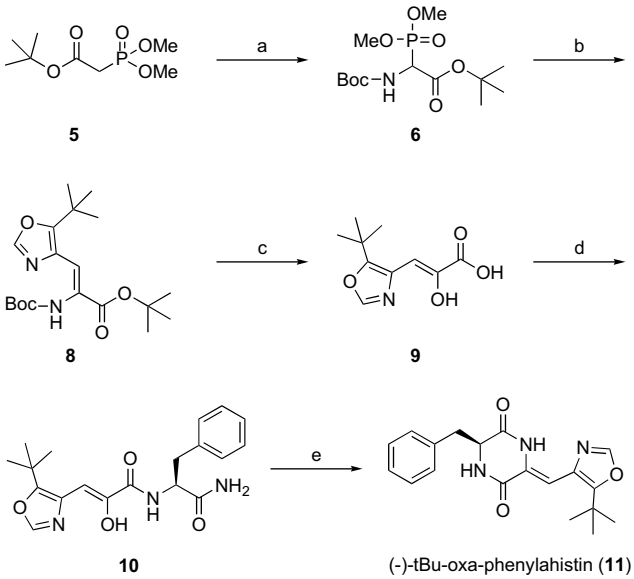
Table 3
MonodehydroDKP formation from a β-phenyl-α-keto acid derivative



3d **4d**

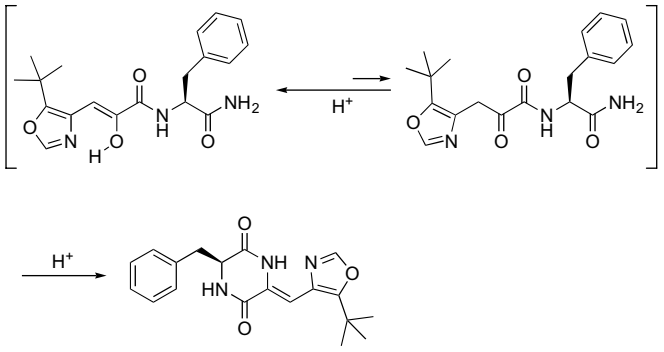
Entry	*p*-TsOH (mol %)	Time (h)	Yield (%)[a]	ee (%)[b]
1	1	18	20	>99[c]
2	1	48	31	>99[c]
3	5	6	34	>99[c]
4	5	18	35	74
5	10	3	5	>99[c]
6	10	6	38	59

[a] Isolated yield.
[b] Enantiomeric excess values were determined by chiral HPLC using CHIRALCEL OD column eluted with *n*-hexane/ethanol (5:1).
[c] No another enantiomer was detected.



5 **6** **8** **9** **10** (-)-tBu-oxa-phenylahistin (**11**)

Scheme 2. Synthesis of a phenylahistin derivative **11** ((−)-*tert*-butyl-oxa-phenylahistin) via acid catalyzed monodehydroDKP synthesis. Reagents and conditions; (a) (i) NaH, TsN_3, rt, 2 h, (ii) Boc-NH_2, cat. $Rh_2(OAc)_4$, toluene, reflux, 1 h, 51% in two steps; (b) 5-*tert*-butyl-4-oxazolecarboxaldehyde **7**, Cs_2CO_3, DMF, rt, 14 h, 47%; (c) 4 M HCl/dioxane, rt, 1 h, 76%; (d) HCl·H-Phe-NH_2, EDC·HCl, HOBt·H_2O, Et_3N, DMF, rt, 14 h, 43%; (e) 5 mol % *p*-TsOH, toluene, reflux, 6 h, 20%.



Scheme 3. Keto–enol tautomerism of β-aryl-α-keto acid derivative.

dioxane to produce corresponding acid **9**.[15] This β-aryl-α-hydroxyacrylic acid **9** was then condensed with H-Phe-NH_2 by the EDC–HOBt method to afford *N*-(β-aryl)-α-hydroxyacryloyl-Phe-NH_2 **10**. Finally, the acid catalyzed intramolecular cyclization reaction in the presence of 5 mol % *p*-TsOH for 6 h was performed to give desired (−)-*tert*-butyl-oxa-phenylahistin **11** with no racemization (>99% ee), although the chemical yield of the final step was low (20%). Total yield of **11** from commercially available starting material **5** was 2%. Compound **11** exhibited mild cytotoxic activity with IC_{50} value of 924 nM against HT-29 human colon cancer cell lines.

2.5. Low reactivity in β-aryl-α-ketoacyl amino acid derivatives

Observed low reactivity in β-aryl-α-keto acid derivative was surely caused by keto-enol tautomerism at the α-keto acid moiety with β-aromatic ring (Scheme 3), i.e., an unfavorable enol form for the cyclization was stabilized by conjugation with the aromatic ring. Actually, from the NMR analysis, it was indicated that these substrates existed as enol forms with conjugation to the β-aryl groups (for example, compounds **9** and **10**, see Experimental). These enol forms are inconvenient to accept a nucleophilic attack of the amide nitrogen (Scheme 3), hence, resulted in the observed low reactivity. Elongated reaction time in the presence of acids enhanced the racemization at the α-position of the amino acid. Furthermore, catalytic amount of acid not only promotes the monodehydroDKP formation, but also would accelerate the enol formation through protonation to the α-carbonyl oxygen in the β-aryl-α-keto acid moiety. Reaction conditions that are able to accelerate the keto formation might be effective to solve this problem, which should be considered in the future study.

However, it is certain that this method is beneficial for the synthesis of monodehydroDKPs from β-aliphatic-α-ketoacyl amino acid derivatives, likely to be applied to combinatorial synthesis of monodehydroDKP derivatives in the future. Additionally, 6-methylene-2,5-piperazinedione **12** derivatives (Fig. 2) synthesized in this new synthetic method would be a valuable key synthon for the synthesis of naturally occurring monodehydroDKPs based on the derivatization from the *exo*-methylene structure.

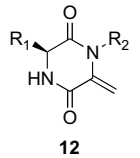


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Figure 2. MonodehydroDKP synthon with an *exo*-olefin structure.

3. Conclusion

We have developed a new synthetic method for monodehydroDKPs with no or slight racemization, which was based on an acid catalyzed intramolecular cyclization of *N*-α-ketoacyl amino acid amides. The catalytic use of *p*-TsOH (3–5 mol %) with a pK_a value of −6.57 was superior for this cyclization reaction. In case β-aliphatic-α-ketoacyl amino acid amides were used as starting materials, no racemization was observed. In case of a β-aryl-α-ketoacyl phenylalanine amide, corresponding monodehydroDKP could be obtained by optimizing the reaction condition (5 mol % *p*-TsOH, reflux for 6 h) although the chemical yield was mild. We applied this optimized reaction condition to the synthesis of (−)-*tert*-butyl-oxa-phenylahistin, which is a derivative of natural anti-microtubule agent phenylahistin, and successfully synthesized it. These findings suggest that this method is beneficial for the convenient synthesis of monodehydroDKPs. It is likely to be applied to combinatorial synthesis of monodehydroDKP derivatives in the future.

4. Experimental

4.1. General procedures

Melting points were measured on a Yanagimoto micro hot-stage apparatus and are uncorrected. Proton (^{1}H) NMR spectra were recorded on either a JEOL JNM-AL300 spectrometer operating at 300 MHz for proton. Chemical shifts were recorded as δ values in parts per million (ppm) downfield from tetramethylsilane (TMS). Low- and high-resolution mass spectra were recorded on a JEOL JMS-GCmate (EI, CI) or a Micromass LCT (ESI). Optical rotations were measured with a Horiba High-speed Accurate Polarimeter SEPA-300 at the sodium-D line (589 nm) at the concentrations (*c*, g/100 mL). The measurements were carried out between 22 and 28 °C in a cell with path length (*l*) of 0.5 dm. Specific rotations $[\alpha]_D$ are given in 10^{-1} deg cm^2 g^{-1}. Preparative HPLC was performed using a C18 reverse-phase column (19×100 mm; SunFire™ Prep C18 OBD™ 5 μm) with binary solvent system: linear gradient of CH_3CN in 0.1% aqueous TFA at a flow rate of 15 mL/min, detected at UV 230 nm. Analytical HPLC was performed using a C18 reverse-phase column (4.6×150 mm; YMC Pack ODS AM302) with a binary solvent system: (a linear gradient of CH_3CN and aq TFA (0.1%) at a flow rate of 0.9 mL min^{-1}), detected at 230 nm. The t_R given for the target compounds are obtained from analytical HPLC. Solvents used for HPLC were of HPLC grade and all other chemicals were of analytical grade or better.

*4.1.1. N-2-Oxo-propanoyl-L-phenylalanine amide (**3a**) (general method for the synthesis of N-α-ketoacyl amino acid amides, **3a–d**)*

A suspension of HCl·H-Phe-NH_2 (1.0 g, 4.98 mmol) in DCM (49 mL) was neutralized with Et_3N (0.69 mL, 4.98 mmol) at 4 °C. To this mixture were added HOBt·H_2O (0.76 g, 4.98 mmol), pyruvic acid (0.52 mL, 7.47 mmol), and EDC·HCl (1.05 g, 5.47 mmol), and the mixture was stirred at 4 °C for 30 min and at room temperature for 2 h. After removal of the solvent in vacuo, the residue was dissolved in AcOEt, successively washed with 10% citric acid, 5% $NaHCO_3$, and saturated NaCl for three times, dried over Na_2SO_4, and concentrated in vacuo to obtain 0.76 g (65%) of the title compound as a white solid. Mp 138–140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (d, *J*=8.6 Hz, 1H), 7.52 (s, 1H), 7.24–7.19 (m, 6H), 4.45–4.37 (m, 1H), 3.11 (dd, *J*=4.2, 13.8 Hz, 1H), 2.96 (dd, *J*=9.5, 13.8 Hz, 1H), 2.26 (s, 3H); HRMS (EI): *m*/*z* 234.1008 (M^+) (calcd for $C_{12}H_{14}N_2O_3$: 234.1004); $[\alpha]_D^{25}$ −14.8 (*c* 1.03, $CHCl_3$).

*4.1.2. N-2-Oxo-butanoyl-L-phenylalanine amide (**3b**)*

The title compound was prepared according to the same procedure as described in example **3a** using 2-oxobutanoic acid

instead of pyruvic acid. White solid (94%); mp 121–123 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (d, J=8.5 Hz, 1H), 7.53 (s, 1H), 7.24–7.19 (m, 6H), 4.43 (ddd, J=4.4, 8.5, 9.6 Hz, 1H), 3.10 (dd, J=4.5, 13.8 Hz, 1H), 2.96 (dd, J=9.6, 13.8 Hz, 1H), 2.72 (q, J=7.2 Hz, 2H), 0.92 (t, J=7.2 Hz, 3H); HRMS (EI): m/z 248.1157 (M^+) (calcd for $C_{13}H_{16}N_2O_3$: 248.1161); $[\alpha]_D^{25}$ −22.9 (c 1.02, $CHCl_3$).

*4.1.2.1. N-2-Oxo-3-methylbutanoyl-L-phenylalanine amide (**3c**).* The title compound was prepared according to the same procedure as described in example **3a** using 3-methyl-2-oxobutanoic acid instead of pyruvic acid. White solid (74%); mp 166–168 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (d, J=8.7 Hz, 1H), 7.55 (s, 1H), 7.24–7.19 (m, 6H), 4.50 (ddd, J=4.2, 8.7, 9.9 Hz, 1H), 3.23 (dq, J=6.9, 6.9 Hz, 1H), 3.10 (dd, J=4.2, 13.6 Hz, 1H), 2.92 (dd, J=9.9, 13.6 Hz, 1H), 0.96 (d, J=6.9 Hz, 3H), 0.87 (d, J=6.9 Hz, 3H); HRMS (EI): m/z 262.1311 (M^+) (calcd for $C_{14}H_{18}N_2O_3$: 262.1317); $[\alpha]_D^{25}$ −13.8 (c 1.03, $CHCl_3$).

*4.1.3. N-2-Oxo-3-phenylpropanoyl-L-phenylalanine amide (**3d**)*

The title compound was prepared according to the same procedure as described in example **3a** using 3-phenyl-2-oxobutanoic acid instead of pyruvic acid. White solid (66%); mp 123–125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J=7.7 Hz, 1H), 7.34–7.01 (m, 10H), 5.83 (s, 1H), 5.75 (s, 1H), 4.61 (ddd, J=6.9, 6.9, 7.7 Hz, 1H), 4.15 (s, 2H), 3.08 (dd, J=2.0, 6.9 Hz, 2H); HRMS (EI): m/z 310.1318 (M^+) (calcd for $C_{18}H_{18}N_2O_3$: 310.1317).

*4.1.3.1. (S)-3-Benzyl-6-methylenepiperazine-2,5-dione (**4a**).* Using a Dean–Stark trap whose trap part was filled with molecular sieves 3 Å, a solution of *N*-2-oxo-propanoyl-L-phenylalanine amide from example **3a** (100 mg, 0.427 mmol) in toluene (20 mL) was refluxed in the presence of *p*-TsOH·H_2O (4.37 mg, 0.023 mmol, 0.05 equiv) for 18 h. After removal of the solvent, the residue was triturated in ether to obtain 89 mg (96%) of the title compound as a white solid. Mp 175–177 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.41 (s, 1H), 7.24–7.11 (m, 5H), 4.90 (s, 1H), 4.50 (s, 1H), 4.40–4.37 (m, 1H), 3.15 (dd, J=3.8, 13.5 Hz, 1H), 2.91 (dd, J=5.0, 13.5 Hz, 1H); HRMS (EI): m/z 216.0891 (M^+) (calcd for $C_{12}H_{12}N_2O_2$: 216.0899); $[\alpha]_D^{26}$ −40.0 (c 1.08, DMSO). Enantiomeric excess was determined to be >99% using chiral HPLC with a CHIRALCEL OD column.

*4.1.4. (S,Z)-3-Benzyl-6-ethylidenepiperazine-2,5-dione (**4b**)*

The title compound was prepared according to example **4a** using the compound of example **3b**. White solid (86%); mp 219–221 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.20 (s, 1H), 7.25–7.12 (m, 5H), 5.50 (q, J=7.5 Hz, 1H), 4.32–4.29 (m, 1H), 3.12 (dd, J=4.2, 13.5 Hz, 1H), 2.90 (dd, J=5.0, 13.5 Hz, 1H), 1.52 (d, J=7.5 Hz, 3H); HRMS (EI): m/z 230.1057 (M^+) (calcd for $C_{13}H_{14}N_2O_2$: 230.1055); $[\alpha]_D^{26}$ −111.1 (c 1.03, DMSO). Enantiomeric excess was determined to be >99% using chiral HPLC with a CHIRALCEL OD column.

*4.1.5. (S)-3-Benzyl-6-(propan-2-ylidene)piperazine-2,5-dione (**4c**)*

The title compound was prepared according to example **4a** using the compound of example **3c**. White solid (94%); mp 255–257 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.26 (s, 1H), 7.97 (d, J=3.3 Hz, 1H), 7.56–7.10 (m, 5H), 4.04 (m, 1H), 3.00 (dd, J=4.4, 13.5 Hz, 1H), 2.85 (dd, J=5.3, 13.5 Hz, 1H), 1.8 (s, 3H), 1.49 (s, 3H); HRMS (EI): m/z 244.1210 (M^+) (calcd for $C_{14}H_{16}N_2O_2$: 244.1212); $[\alpha]_D^{26}$ −112.8 (c 0.50, DMSO). Enantiomeric excess was determined to be >99% using chiral HPLC with a CHIRALCEL OD column.

*4.1.6. (S,Z)-3-Benzyl-6-benzylidenepiperazine-2,5-dione (**4d**)*

The title compound was prepared according to example **4a** using the compound of example **3c**. Off white solid (35%); mp 275–276 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.46 (s, 1H), 7.46–7.13 (m, 10H), 6.33 (s, 1H), 4.36 (m, 1H), 3.15 (dd, J=3.9, 13.4 Hz, 1H), 2.95 (dd, J=4.9, 13.4 Hz, 1H); HRMS (EI): m/z 292.1211 (M^+) (calcd for $C_{18}H_{16}N_2O_2$: 292.1212); $[\alpha]_D^{25}$ −316.2 (c 0.62, DMSO). Enantiomeric excess was determined to be 73% using chiral HPLC with a CHIRALCEL OD column.

*4.1.7. N-2-Oxo-propanoyl-L-phenylalanine benzylamide (**3e**)*

A solution of HCl·H-Phe-NH-benzyl (215 mg, 0.85 mmol) in DMF was neutralized with Et_3N (122 μL, 0.85 mmol) at 4 °C. To this mixture were added HOBt·H_2O (129 mg, 0.85 mmol), pyruvic acid (116 mg, 1.26 mmol), and EDC·HCl (242 mg, 1.26 mmol), and the mixture was stirred at room temperature for 2 h. After removal of the solvent in vacuo, the residue was dissolved in AcOEt, successively washed with 10% citric acid, 5% $NaHCO_3$, and saturated NaCl for three times, dried over Na_2SO_4, and concentrated in vacuo to obtain 175 mg (64%) of the title compound as a off white solid. Mp 122–124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J=8.4 Hz, 1H), 7.27–7.03 (m, 10H), 5.80 (br s, 1H), 4.48–4.58 (m, 1H), 4.24–4.41 (m, 2H), 3.01–3.18 (m, 2H), 2.49 (s, 3H); HRMS (EI): m/z 324.1470 (M^+) (calcd for $C_{19}H_{20}N_2O_3$: 324.1474); $[\alpha]_D^{26}$ −13.3 (c 1.06, $CHCl_3$).

*4.1.8. N-2-Oxo-propanoyl-L-phenylalanine isopropylamide (**3f**)*

The title compound was prepared according to example **3e** using HCl·H-Phe-NH-isopropyl. Yield 73%. Off white solid; mp 138–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J=7.2 Hz, 1H), 7.21–7.34 (m, 5H), 5.09 (d, J=7.0 Hz 1H), 4.36–4.45 (m, 1H), 3.88–4.01 (m, 1H), 3.13 (dd, J=5.9, 13.4 Hz, 1H), 2.97 (dd, J=9.0, 13.4 Hz, 1H), 2.46 (s, 3H), 1.03 (d, J=6.6 Hz, 3H), 0.91 (d, J=6.6 Hz, 3H); HRMS (EI): m/z 276.1472 (M^+) (calcd for $C_{15}H_{20}N_2O_3$: 276.1474); $[\alpha]_D^{25}$ −14.8 (c 1.05, $CHCl_3$).

*4.1.9. N-2-Oxo-propanoyl-L-phenylalanine isobutylamide (**3g**)*

The title compound was prepared according to example **3e** using HCl·H-Phe-NH-isobutyl. Yield 57%. Brown solid; mp 114–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J=8.1 Hz, 1H), 7.20–7.34 (m, 5H), 5.46 (br s, 1H), 4.47 (ddd, J=6.3, 8.1, 8.4 Hz, 1H), 3.12 (dd, J=6.3, 13.5 Hz, 1H), 3.04 (dd, J=8.4, 13.5 Hz, 1H), 2.89–3.04 (m, 2H), 2.45 (s, 3H), 1.54–1.67 (m, 1H), 0.76 (d, J=6.8 Hz, 3H), 0.74 (d, J=6.8 Hz, 3H); HRMS (EI): m/z 290.1636 (M^+) (calcd for $C_{16}H_{22}N_2O_3$: 290.1630); $[\alpha]_D^{26}$ −23.9 (c 1.03, $CHCl_3$).

*4.1.10. N-2-Oxo-propanoyl-L-phenylalanine allylamide (**3h**)*

The title compound was prepared according to example **3e** using HCl·H-Phe-NH-allyl. Yield 40%. Brown solid; mp 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (br d, J=8.4 Hz, 1H), 7.34–7.19 (m, 5H), 5.71–5.55 (m, 1H), 5.58 (br s, 1H), 5.09–4.96 (m, 2H), 4.55–4.47 (m, 1H), 3.81–3.75 (m, 2H), 3.17–3.02 (m, 2H), 2.44 (s, 3H); HRMS (EI): m/z 274.1325 (M^+) (calcd for $C_{15}H_{18}N_2O_3$: 274.1317); $[\alpha]_D^{26}$ −26.1 (c 1.00, $CHCl_3$).

*4.1.11. N-2-Oxo-propanoyl-L-leucine allylamide (**3i**)*

The title compound was prepared according to example **3e** using HCl·H-Leu-NH-allyl. White solid (63%); mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (br s, 1H), 6.01 (br s, 1H), 5.88–5.75 (m, 1H), 5.21–5.13 (m, 2H), 4.39–4.32 (m, 1H), 3.90–3.86 (m, 2H), 2.48 (s, 3H), 1.78–1.60 (m, 3H), 0.95 (d, J=5.2 Hz, 3H), 0.93 (d, J=5.2 Hz, 3H); HRMS (ESI): m/z 241.1530 ($M+H^+$) (calcd for $C_{12}H_{21}N_2O_3$: 241.1552); $[\alpha]_D^{26}$ −8.1 (c 1.00, $CHCl_3$).

*4.1.12. N-2-Oxo-propanoyl-L-serine(Bzl) allylamide (**3j**)*

The title compound was prepared according to example **3e** using HCl·H-Ser(Bzl)-NH-allyl. Yield 86%. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J=6.4 Hz, 1H), 7.29–7.36 (m, 5H), 6.37 (br s, 1H), 5.74–5.87 (m, 1H), 5.11–5.19 (m, 2H), 4.46–4.63 (m, 3H), 3.88–3.93 (m, 3H), 3.56 (dd, J=7.4, 9.1 Hz, 1H), 2.47 (s, 3H); HRMS

(ESI): *m*/*z* 305.1526 ($M+H^+$) (calcd for $C_{16}H_{21}N_2O_4$: 305.1501); $[\alpha]_D^{25}$ −1.4 (*c* 0.79, $CHCl_3$).

4.1.13. (S)-1,3-Dibenzyl-6-methylenepiperazine-2,5-dione (**4e**)

Using a Dean–Stark trap whose trap part was filled with molecular sieves 4 Å, a solution of *N*-2-oxo-propanoyl-L-phenylalanine benzylamide from example **3e** (100 mg, 0.31 mmol) in toluene (20 mL) was refluxed in the presence of *p*-TsOH·H_2O (1.8 mg, 0.0093 mmol, 0.03 equiv) for 24 h. After removal of the solvent, the residue was purified by a silica gel chromatography to yield 50 mg (53%) of title compound as a white solid. Mp 124–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01–7.35 (m, 10H), 6.84 (br s, 1H), 5.60 (s, 1H), 5.01 (d, *J*=15.7 Hz, 1H), 4.85 (d, *J*=15.7 Hz, 1H), 4.76 (s, 1H), 4.49–4.52 (m, 1H), 3.36 (dd, *J*=3.7, 13.6 Hz, 1H), 3.12 (dd, *J*=7.7, 13.6 Hz, 1H); HRMS (EI): *m*/*z* 306.1369 (M^+) (calcd for $C_{19}H_{18}N_2O_2$: 306.1368); $[\alpha]_D^{26}$ −433.1 (*c* 0.19, $CHCl_3$). Enantiomeric excess was determined to be >99% using chiral HPLC with a CHIRALCEL OD column.

4.1.14. (S)-3-Benzyl-1-isopropyl-6-methylenepiperazine-2,5-dione (**4f**)

The title compound was prepared according to example **4e** using the compound from example **3f**. Yield 20%. Mp 141–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.27 (m, 3H), 7.18–7.16 (m, 2H), 5.87 (br s, 1H), 5.61 (s, 1H), 4.90 (s, 1H), 4.47–4.38 (m, 1H), 4.29–4.22 (m, 1H), 3.23 (dd, *J*=5.7, 13.6 Hz, 1H), 3.00 (dd, *J*=5.7, 13.6 Hz, 1H), 1.41 (dd, *J*=5.0, 7.0 Hz, 6H); HRMS (ESI): *m*/*z* 259.1464 ($M+H^+$) (calcd for $C_{15}H_{19}N_2O_2$: 259.1447); $[\alpha]_D^{26}$ −122.7 (*c* 0.18, $CHCl_3$). Enantiomeric excess was determined to be >99% using chiral HPLC with a CHIRALCEL OD column.

4.1.15. (S)-3-Benzyl-1-isobutyl-6-methylenepiperazine-2,5-dione (**4g**)

The title compound was prepared according to example **4e** using the compound from example **3g**. Yield 43%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17–7.36 (m, 5H), 5.91 (br s, 1H), 5.73 (d, *J*=1.5 Hz, 1H), 4.84 (s, 1H), 4.30–4.37 (m, 1H), 3.65 (dd, *J*=8.1, 13.8 Hz, 1H), 3.55 (dd, *J*=6.9, 13.8 Hz, 1H), 3.37 (dd, *J*=3.6, 13.8 Hz, 1H), 2.93 (dd, *J*=9.0, 13.5 Hz, 1H), 1.98–2.13 (m, 1H), 0.92 (d, *J*=5.7 Hz, 3H), 0.90 (d, *J*=5.7 Hz, 3H); HRMS (EI): *m*/*z* 324.1470 (M^+) (calcd for $C_{19}H_{20}N_2O_3$: 324.1474); $[\alpha]_D^{26}$ −93.5 (*c* 0.48, $CHCl_3$). Enantiomeric excess was determined to be >99% using chiral HPLC with a CHIRALCEL OD column.

4.1.16. (S)-1-Allyl-3-benzyl-6-methylenepiperazine-2,5-dione (**4h**)

The title compound was prepared according to example **4e** using the compound from example **3h**. Yield 92%. Mp 102–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–7.35 (m, 5H), 6.48 (br s, 1H), 5.63–5.77 (m, 1H), 5.65 (s, 1H), 5.21 (d, *J*=10.2 Hz, 1H), 5.10 (d, *J*=17.4 Hz, 1H), 4.84 (s, 1H), 4.36–4.48 (m, 2H), 4.25 (br d, *J*=16.2 Hz, 1H), 3.27–3.38 (m, 1H), 2.94–3.08 (m, 1H); HRMS (EI): *m*/*z* 256.1210 (M^+) (calcd for $_{15}H_{16}N_2O_2$: 256.1212); $[\alpha]_D^{25}$ −320.6 (*c* 0.15, $CHCl_3$). Enantiomeric excess was determined to be >99% using chiral HPLC with a CHIRALCEL OD column.

4.1.17. (S)-1-Allyl-3-(iso-butyl)-6-methylenepiperazine-2,5-dione (**4i**)

The title compound was prepared according to example **4e** using the compound from example **3i**. Yield 96%. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (br s, 1H), 5.73–5.85 (m, 1H), 5.8 (d, *J*=1.3 Hz, 1H), 5.24 (dd, *J*=16, 1.2 Hz, 1H), 5.19 (dd, *J*=24, 1.2 Hz, 1H), 5.00 (s, 1H), 4.49–4.56 (m, 1H), 4.26 (dd, *J*=5.2, 16 Hz, 1H), 4.13–4.20 (m, 1H), 1.66–1.83 (m, 3H), 0.98 (d, *J*=6.0 Hz, 3H), 0.97 (d, *J*=6.0 Hz, 3H); HRMS (ESI): *m*/*z* 223.1457 ($M+H^+$) (calcd for $C_{12}H_{19}N_2O_2$: 223.1447); $[\alpha]_D^{26}$ −122.7 (*c* 0.18, $CHCl_3$). Enantiomeric excess was determined to be >99% using chiral HPLC with a CHIRALCEL OD column.

4.1.18. (S)-1-Allyl-3-(benzyloxy)methyl-6-methylenepiperazine-2,5-dione (**4j**)

The title compound was prepared according to example **4e** using the compound from example **3j**. Yield 69%. Brown solid; mp 78–81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.37 (m, 5H), 6.76 (br s, 1H), 5.81 (d, *J*=1.4 Hz, 1H), 5.68–5.79 (m, 1H), 5.18–5.20 (m, 1H), 5.15 (dd, *J*=6.5, 0.9 Hz, 1H), 4.95 (s, 1H), 4.53 (s, 2H), 4.47–4.50 (m, 1H), 4.32–4.34 (m, 1H), 4.20–4.27 (m, 1H), 3.75–3.85 (m, 2H); HRMS (ESI): *m*/*z* 287.1400 ($M+H^+$) (calcd for $C_{16}H_{19}N_2O_3$: 287.1396); $[\alpha]_D^{26}$ −107.4 (*c* 0.25, $CHCl_3$). Enantiomeric excess was determined to be >99% using chiral HPLC with a CHIRALCEL OD column.

4.1.19. N-tert-Butoxycarbonyl-α-dimethylphosphonoglycine-tert-butyl ester (**6**)

The solution of *tert*-butyl-*P*,*P*-dimethylphosphonoacetate (12.5 mL, 63 mmol, 1.0 equiv) in THF (20 mL) was added dropwise to a solution of NaH (60% NaH, 2.7 g, 69.3 mmol, 1.1 equiv) in anhydrous THF (300 mL) at 0 °C. After the mixture was stirred for 45 min at the same temperature, a solution of TsN_3 (12.4 g, 63 mmol, 1.0 equiv) in THF (10 mL) was added dropwise at 0 °C. The cooling bath was removed and the mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of ether/H_2O (1:1, 200 mL) at 4 °C. After the resultant organic phase was washed with water, 10% $NaHCO_3$, and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. The residual oil was purified by a silica gel column chromatography to yield 9.9 g (63%) of diazo phoaphonoacetate as a yellow oil. This oil was used in the next reaction. Boc–NH_2 (18.3 g, 156 mmol, 4.0 equiv) was added to a solution of diazo compound (9.8 g, 39 mmol, 1.0 equiv) in toluene (200 mL), and the mixture was refluxed in the presence of $Rh_2(OAc)_4$ (346 mg, 0.78 mmol, 0.02 equiv) for 1 h using a Dean–Stark trap. After removal of the solvent, the residue was dissolved in AcOEt, successively washed with 10% citric acid, 5% $NaHCO_3$, and saturated NaCl for three times, dried over Na_2SO_4, and concentrated in vacuo. The residual oil was purified by a silica gel column chromatography to yield 11 g (81%) of a title compound as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (d, *J*=8.4 Hz, 1H), 4.76 (dd, *J*=9.2, 21.7 Hz, 1H), 3.82 (dd, *J*=1.8, 11.0 Hz, 6H), 1.51 (s, 9H), 1.45 (s, 9H); HRMS (CI): *m*/*z* 340.1526 (M^+) (calcd for $C_{13}H_{27}NO_7$: 340.1525).

4.1.20. tert-Butyl 1-(tert-butoxycarbonyl)-2-(5-tert-butyloxazol-4-yl)vinylcarbamate (**8**)

To a solution of *N*-(*tert*-butoxycarbonyl)-α-dimethylphosphonoglycine-*tert*-butyl ester **6** (11.8 g, 34.68 mmol) and 5-*tert*-butyloxazole-4-carboxaldehyde **7** (6.9 g, 45.08 mmol) in DMF (50 mL) was added Cs_2CO_3 (12.4 g, 38.15 mmol) under an argon atmosphere at room temperature. The reaction mixture was stirred for 14 h at room temperature. After removal of solvent in vacuo, the residue was dissolved in AcOEt, successively washed with 10% citric acid, 5% $NaHCO_3$, and saturated NaCl for three times, dried over Na_2SO_4, and concentrated in vacuo. The residual oil was purified by a silica gel column chromatography to yield 6.0 g (47%) of title compound as a white solid. Mp 170–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 6.55 (s, 1H), 1.54 (s, 9H), 1.49 (s, 9H), 1.38 (s, 9H); HRMS (EI): *m*/*z* 366.2159 (M^+) (calcd for $C_{19}H_{30}N_2O_5$: 366.2154).

4.1.21. 3-(5-tert-Butyloxazol-4-yl)-2-hydroxyacrylic acid (**9**)

The compound from example **8** (6.0 g, 16.3 mmol) was treated with 4 M HCl/dioxane (64 mL) for 1 h at room temperature. After removal of the solvent, the residue was dissolved in AcOEt, washed with 5% citric acid, and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to obtain 2.6 g (76%) of the title compound as a white solid. Mp 153–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 6.78 (s, 1H), 1.41 (s, 9H); HRMS (EI): *m*/*z* 211.0841 (M^+) (calcd for $C_{10}H_{13}NO_4$: 211.0844).

*4.1.22. 3-(5-tert-Butyloxazol-4-yl)-N-((S)-1-carbamoyl-2-phenylethyl)-2-hydroxyacrylamide (**10**)*

To a solution of the compound from example **9** (2.61 g, 12.3 mmol) in DMF were added $HOBt\cdot H_2O$ (2.26 g, 14.76 mmol), $EDC\cdot HCl$ (2.8 g, 14.76 mmol), $HCl\cdot$H-Phe-NH_2 (3.16 g, 14.76 mmol), and Et_3N (1.72 mL, 12.3 mmol), and the reaction mixture was stirred for 14 h at room temperature. After removal of the solvent, the residue was dissolved in AcOEt, successively washed with 10% citric acid, 5% $NaHCO_3$, and saturated NaCl for three times, dried over Na_2SO_4, and concentrated in vacuo to obtain the title compound. Yield 2.26 g (43%); mp 50–53 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.04 (s, 1H), 7.81 (d, J=0.6 Hz 1H), 7.74–7.21 (m, 5H), 6.62 (d, J=0.7 Hz, 1H), 6.00 (s, 1H), 5.52 (s, 1H), 4.79–4.72 (m, 1H), 3.24–3.11 (m, 2H), 1.38 (s, 9H); HRMS (EI): m/z 357.1689 (M^+) (calcd for $C_{19}H_{23}N_3O_4$: 357.1688).

*4.1.23. (S,Z)-3-[(5-tert-Butyloxazol-4-yl)methylene]-6-benzylpiperazine-2,5-dione (**11**)*

Using a Dean–Stark trap whose trap part was filled with molecular sieves 3 Å, a solution of the compound from example **10** (50 mg, 0.14 mmol) in toluene (5 mL) was refluxed in the presence of *p*-TsOH (1.3 mg, 0.007 mmol) for 6 h. After removal of the solvent, the residue was purified by HPLC to obtain the title compound as a white powder. Yield 8.1 mg (20%), mp 52–56 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.65 (s, 1H), 8.60 (s, 1H), 8.47 (s, 1H), 7.24–7.13 (m, 5H), 6.37 (s, 1H), 4.52 (m, 1H), 3.20 (dd, J=3.7, 13.6 Hz, 1H), 2.95 (dd, J=5.0, 13.6 Hz, 1H), 1.31 (s, 9H); HRMS (EI): m/z 339.1584 (M^+) (calcd for $C_{19}H_{21}N_3O_3$: 339.1583); $[\alpha]_D^{25}$ −128.9 (c 0.27, DMSO). Enantiomeric excess was determined to be >99% using chiral HPLC with a CHIRALCEL OD column.

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Supplementary data

Supplementary data include the monodehydroDKP formation by base-catalyzed method and chiral HPLC charts of the acid catalyzed reaction from compound **3d**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.02.058.

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