

Synthesis and Conformational Study of Ser and Cys Derivatives of *N*-Hydroxy Diketopiperazine

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N-Hydroxy diketopiperazine derivatives from L- and D-forms of Ser and Cys were synthesized for the first time and the ring conformation of both analogues in water was determined to be close to flat *via* NMR and *ab initio* calculations. However, the side chain of the Ser analogue was oriented toward a pseudo-equatorial position while that of the Cys analogue was slightly oriented toward a pseudo-axial direction, with a slightly distorted boat-shaped ring conformation. Among them, the D-Cys analogue was found to be a weak inhibitor of α -glucosidase.

Key Words : *N*-Hydroxy diketopiperazine, Serine, Cysteine, Conformation, Glucosidase

Introduction

2,5-Diketopiperazines, known as cyclic dipeptides, are frequently formed from both the enzymatic and nonenzymatic processes of peptides/proteins.¹ They are also well-known as by-products that are formed during removal of the temporal protecting group of the second amino acid.² Many cyclic dipeptides are found in nature and their derivatives show interesting biological activities,³ including antiviral,⁴ antifungal,⁵ antitumour,⁶ antithrombotic⁷ and antibacterial⁸ properties. *N*-Hydroxylation of diketopiperazines is a known biological process in the protist and plant kingdoms during the syntheses of iron chelators and dehydro amino acids. Natural products like aspergillilic acid,⁹ pulcherriminic acid,¹⁰ and sarcodonin¹¹ contain several structural features of *N*-hydroxy diketopiperazine and it is likely that they are the oxidized metabolites or intermediates of diketopiperazine derivatives.^{1,12}

Although various syntheses of racemic *N*-hydroxy diketopiperazine derivatives have been studied, only a few syntheses of asymmetric *N*-hydroxy analogues have been reported.¹³ More recently, M. Akiyama *et al.* described a convenient synthesis and the spectroscopic properties of *N*-hydroxy diketopiperazines derived from L-forms of Ala, Val, Pro, Phe, and Asp.¹⁴ Early studies, however, revealed that handling these types of compounds is a nontrivial process with low cyclization yields.^{13a} In addition, the purification of a highly polar hydroxamate with a hydrophilic side chain is a problematic step for the synthesis.

Here we report the first synthesis of *N*-hydroxy diketo-

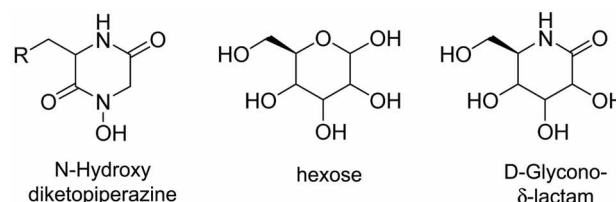
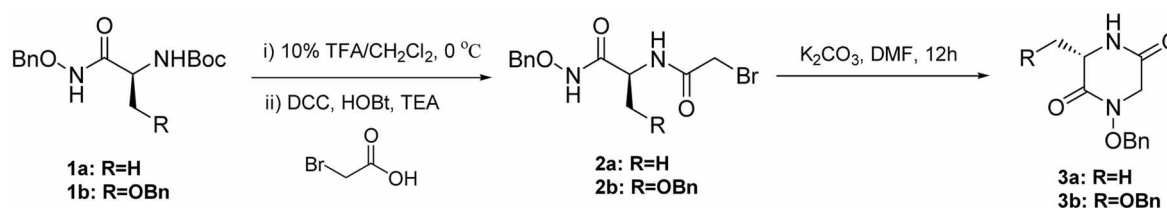


Figure 1. Structural similarities among *N*-hydroxy diketopiperazine, hexose, and D-glycono- δ -lactam.

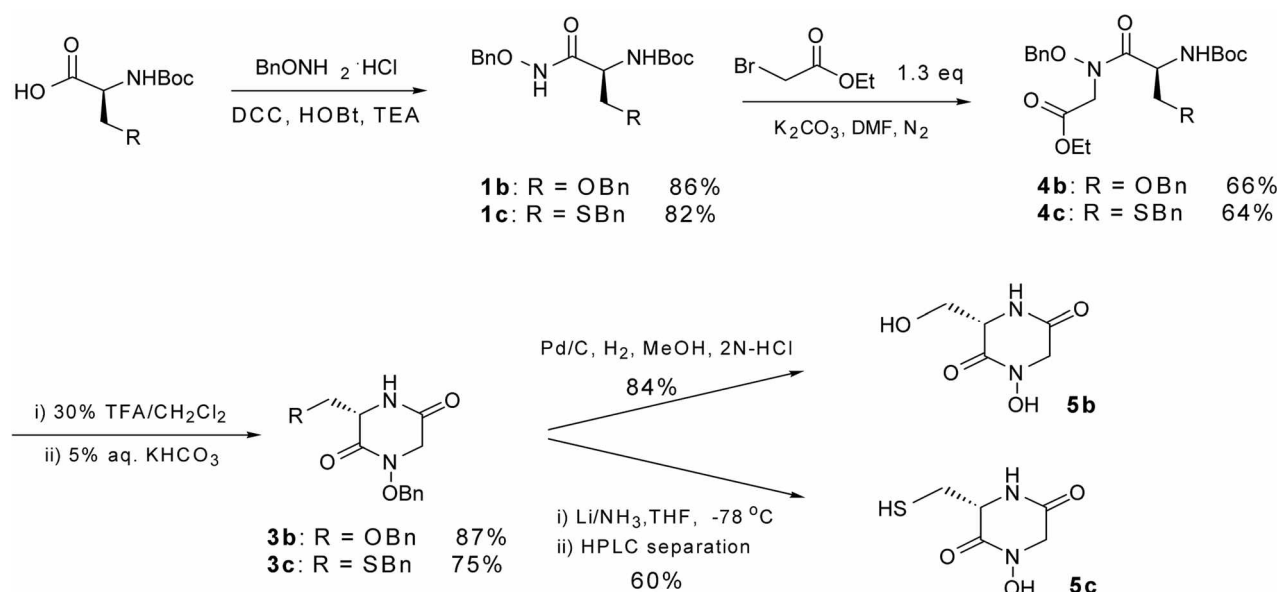
piperazine analogues from L- and D-forms of Ser and Cys, respectively. Nothing has been reported, so far, regarding the synthesis of Ser and Cys analogues or their biological activities. We also determined the preferred conformation *via* NMR and *ab initio* calculations and evaluated inhibitory activities against α -glucosidase because there are some structural similarities between hexose and *N*-hydroxy diketopiperazine, especially from Ser or Cys (Fig. 1). The conformational study of the new *N*-hydroxy diketopiperazines may provide us some background of understanding biological activities. In a study with implications for our compounds, Nishimura's group reported the synthesis and conformational analysis of eight isomers of D-glycono- δ -lactam (Fig. 1).¹⁵ They found that five isomers, including three with boatlike conformations, exhibited inhibitory activities against β -glucosidase.

Results and Discussion

Synthesis. In our synthetic efforts, we first tried the



Scheme 1. Synthesis of protected *N*-hydroxy diketopiperazine derivatives from L-Ala and L-Ser.



Scheme 2. Synthesis of *N*-hydroxy diketopiperazine derivatives from L-Ser and L-Cys analogues.

following strategy (Scheme 1). Starting from Boc-protected L-Ala and L-Ser, we prepared the benzyloxy amides **1a** and **1b** respectively.¹⁶ After removal of the Boc group, bromoacetic acid was attached to give **2a** and **2b** with yields of about 50%. Intramolecular cyclization of the compounds **2a** and **2b** under various basic conditions gave the desired products, **3a** and **3b**, in below 50% yields with decomposed byproducts. Since the yields of the two reactions were unsatisfactory, we modified the synthetic scheme to utilize the cyclization precursors, **4b** and **4c** (Scheme 2).¹⁴

Selective mono *N*-alkylation of the benzyloxy amides, compounds **1b** and **1c**, was successful, giving yields of 64 to 66%. After removal of the Boc-protecting group, the crude product was cyclized under basic conditions to give the diketopiperazine backbones **3b** and **3c**. Deprotection of the benzyl group from the Ser analogue **3b** was accomplished by using Pd/C, H₂, and MeOH in the presence of 2 N HCl. Under the same conditions but without HCl, the monodebenzylated product on the *N*-OH group was obtained. For the Cys derivative **3c**, no product was obtained. By applying Li in liquid NH₃ to the Cys derivatives, debenzylation was complete based on NMR analysis of the crude reaction mixture, but purification step was problematic. Temporary protection of the crude product with Boc group followed by silica gel purification gave the pure bis-protected **5c**. However deprotection of the Boc group under acidic condition (10% TFA in CH₂Cl₂) gave a mixture of desired product and unidentified product having same molecular mass. The pure product **5c** could be obtained only with RP-HPLC purification under an elution of 0.1% TFA in H₂O.

Since the configuration of the stereogenic carbon of the products **5b** and **5c** was opposite to the corresponding natural carbohydrates, D-forms of Ser and Cys were subjected to the same reactions shown in Scheme 2. The yields of the reactions were more or less the same as in the reactions of the L-forms of Ser and Cys derivatives. The

proton NMR data of the enantiomers obtained from L- and D- amino acids were exactly same.

Conformation. Three conformations are known to exist for the diketopiperazine ring and the *N*-hydroxy diketopiperazine ring, depending on the folding angle β : a flat ring conformation ($\beta = 0$), a boat-shaped conformation with a pseudo-axial side chain ($\beta < 0$), and a boat-shaped conformation with a pseudo-equatorial side chain ($\beta > 0$).^{14,17} The preferred conformations of the two compounds, **5b** and **5c**, were determined from *ab initio* calculations with the Gaussian03 package.¹⁸ After generating the conformations of both equatorial and axial side chains with a molecular mechanics-based force field, the *ab initio* structure optimization was carried out with the MP2/6-31G+(d) level in a vacuum. The resulting structures were further optimized in the DMSO solvation environment (dielectric constant = 47.6) with the polarized continuum model (IEFPCM)¹⁹ using the MP2/6-31+(d) level. We also repeated the same calculation with the B3LYP/6-31G+(d) level using the CPCM solvation model.²⁰ This time, the molecule was in the water (dielectric constant = 80) environment and the hydrogen atom at *N*-OH was removed in consideration of the likely protonation state.

As far as the structure was concerned, the lowest energy conformations from two different calculations were essentially the same, with a slightly distorted flat ring as shown in Figure 2. The folding angle β was 5.3 for the Ser analogue **5b** and -5.8 for the Cys analogue **5c**. These results implied that the side chain of **5b** was close to the pseudo-equatorial position, while the side chain of **5c** was closer to the pseudo-axial orientation. Regarding the rotation of side chains, the energy differences among the three rotamers were calculated to be less than 1 kcal/mol.

A NMR study was performed to obtain information on solution conformation. Magnetic nonequivalence for the Gly-CH₂ protons of the two analogues was an indication that

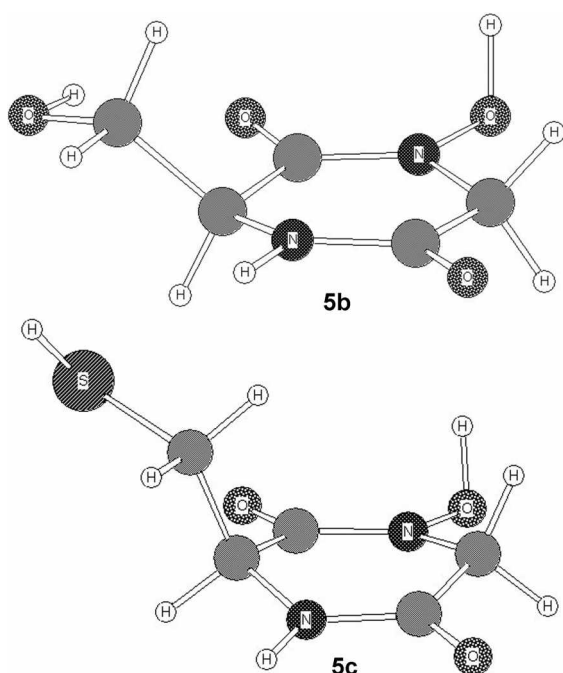


Figure 2. Proposed conformations of the L-Ser analogue **5b** (top) and the L-Cys analogue **5c** (bottom).

Table 1. Proton chemical shifts and coupling constants for **5b** and **5c** in D₂O

Compounds	Gly residue ^a H, H' (² J _{HH'})	Other residue ^b H _a , H _b , H _{b'}
5b	4.34, 4.20 (17.2)	4.11, 3.89, 3.68
5c	4.46, 4.27 (17.2)	4.43, 3.06, 2.85

^aH, H' denote two α -protons of Gly. ^bH_a denotes α -proton, and H_b and H_{b'} denote two β -protons of Ser or Cys.

the ring had a rigid conformation, but distinct differences between the two compounds could not be found (Table 1). In the 2D-NMR study, ROE cross peaks between the two residues (H or H' and H_a, H_b or H_{b'}) were not obtained. Temperature coefficients of the Ser analog in DMSO-*d*₆ was determined to give similar values (4.6×10^{-3} ppm/K for *N*-OH, 4.8×10^{-3} ppm/K for *N*-H, 4.4×10^{-3} ppm/K for O-H), indicating that no intramolecular H-bonded or shielded polar protons are present.

We evaluated the inhibitory activities of synthesized *N*-hydroxy diketopiperazines against rice α -glucosidase. The activities of L-Cys analogue **5c** and its D-Cys analogue enan (**5c**) were very weak with IC₅₀ values of 220 and 100 μ M respectively, while the analogues of L- and D-Ser have no activity. The reason is probably due to the conformational difference from half-chair geometry and the lack of a positive charge at the ring oxygen position, mimicking the transition state of an enzyme-substrate complex.²¹

Conclusion

We prepared new *N*-hydroxy diketopiperazine derivatives from L- and D-forms of Ser and Cys in satisfactory yields.

The ring conformation of both analogues in water was determined to be close to flat via NMR and *ab initio* calculations. However, the side chain of the Ser analogue was oriented toward a pseudo-equatorial position while that of the Cys analogue was slightly oriented toward a pseudo-axial direction, with a slightly distorted boat-shaped ring conformation. Among the compounds we prepared, the D-Cys analogue exhibited very weak activity against rice α -glucosidase.

Experimental Section

General procedures and methods. All reagents were obtained from commercial suppliers and used without purifications unless specified. ¹H and ¹³C-NMR spectra were collected on a Bruker AVANCE II 500 spectrometer at resonance frequencies of 500.1 MHz and 125.7 MHz, respectively. Solvents used were CDCl₃ and D₂O. The chemical shifts were reported in ppm from tetramethylsilane or referenced to solvent on the δ scale. HRMS (FAB) spectra were recorded on a JEOL Ltd. JMS-700 Mstation. The optical rotation was measured on a Rudolph Autopol III automatic polarimeter using Na emission (589 nm). High performance liquid chromatography (HPLC) analyses were performed on a Shimadzu system (LC-10ADVP) with a RI detector (RID-10A). Purification of compound **5c** was carried out by semi-preparative HPLC on a Vydac C18 column (10 \times 250 mm) with a flow rate of 3 mL/min using 0.1% TFA in H₂O as an eluent.

(2-Benzyloxy-1-benzyloxycarbamoyl-ethyl)-carbamic acid *tert*-butyl ester (**1b**)

L-Form: A mixture of Boc-L-Ser(Bzl)-OH (2.4 g, 8.1 mmol), DCC (1.5 g, 7.5 mmol), and HOBt (0.19 mg, 1.3 mmol) was stirred in CH₂Cl₂ (100 mL) at 0 $^{\circ}$ C for 15 min. Subsequently, BnONH₂·HCl (1.0 g, 6.2 mmol) and DIPEA (2.3 mL, 13.2 mmol) were added. After 1 h at 0 $^{\circ}$ C, the mixture was stirred at room temperature for 17 h. The precipitated urea was filtered off and the solution was concentrated *in vacuo*. The residue was dissolved in EtOAc and the precipitated urea was filtered off again. The organic layer was washed with saturated aqueous NaCl solution and dried with MgSO₄. The solvent was removed in *vacuo* and the crude product was purified by chromatography on silica gel column (3:1 hexane/EtOAc) to give a white solid. Yield: 2.14 g (86%). ¹H NMR (500 MHz, CDCl₃): δ 8.93 (bs, 1H), 7.33–7.21 (m, 10H), 5.30 (bs, 1H), 4.87 (s, 2H), 4.49, 4.44 (ABq, *J* = 11.5 Hz, 2H), 4.22 (bs, 1H), 3.79–3.78 (m, 1H), 3.50–3.47 (m, 1H), 1.40 (s, 9H); ¹³C NMR (125.76 MHz, CDCl₃): δ 168.15, 155.34, 137.13, 135.02, 129.14, 128.66, 128.49, 128.44, 127.89, 127.70, 80.34, 78.21, 73.38, 69.38, 52.11, 28.21; HRMS (FAB) *m/z* calculated 401.2076 for C₂₂H₂₉N₂O₅ [M+H]⁺, found 401.2080.

D-Form: By applying the same procedure described above, starting with Boc-D-Ser(Bzl)-OH (2.4 g, 8.1 mmol), the enantiomer of **1b** was obtained. Yield: 2.18 g (88%). ¹H NMR spectrum was the same as for compound **1b**.

(1-Benzyloxycarbamoyl-2-benzylsulfanyl-ethyl)-carbamic

acid *tert*-butyl ester (1c)

L-Form: By using a similar procedure as described above, starting with 2.6 g of Boc-L-Cys(Bzl)-OH, the desired compound was obtained as a white solid. Yield: 2.15 g (82%). ¹H NMR (500 MHz, CDCl₃): δ 9.14 (bs, 1H), 7.38–7.22 (m, 10H), 5.29 (bs, 1H), 4.89 (s, 2H), 4.10 (bs, 1H), 4.49, 4.44 (ABq, *J* = 11.5 Hz, 2H), 2.77–2.67 (m, 2H), 1.42 (s, 9H); ¹³C NMR (125.76 MHz, CDCl₃): δ 168.32, 155.30, 137.72, 134.96, 129.22, 128.95, 128.73, 128.54, 127.20, 80.52, 78.31, 51.69, 36.41, 33.17, 28.23; HRMS (FAB) *m/z* calculated 487.2444 for C₂₆H₃₅N₂O₇ [M+H]⁺, found 487.2455.

D-Form: By applying the same procedure described above, starting with Boc-D-Cys(Bzl)-OH (2.6 g, 8.1 mmol), the enantiomer of **1c** was obtained. Yield: 2.23 g (85%). ¹H NMR spectrum was same as for compound **1c**.

[Benzyloxy-(3-benzyloxy-2-*tert*-butoxycarbonylamino-propionyl)-amino]-acetic acid ethyl ester (4b)

L-Form: To a stirred solution of **1b** (2 g, 5 mmol) and anhydrous K₂CO₃ (1.04 g, 7.5 mmol) in DMF (20 mL) were added dropwise over 30 min ethylbromoacetate (0.72 mL, 6.5 mmol) in DMF (10 mL) at 0 °C under N₂. After 1 h at 0 °C, the mixture was stirred at room temperature for 1 h. Saturated NH₄Cl solution was added to the reaction mixture and then extracted with diethyl ether. The organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel column (3:1 hexane/EtOAc) to give colorless viscous oil. Yield: 1.6 g (66%). ¹H NMR (500 MHz, CDCl₃): δ 7.36–7.25 (m, 10H), 5.41 (d, 1H), 5.03 (bs, 1H), 5.01, 4.96 (ABq, *J* = 10.6 Hz, 2H), 4.54, 4.50 (ABq, *J* = 11.6 Hz, 2H), 4.52, 3.99 (ABq, *J* = 17.6 Hz, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.84–3.81 (m, 1H), 3.74–3.71 (m, 1H), 1.45 (s, 9H), 1.21 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125.76 MHz, CDCl₃): δ 172.97, 167.30, 155.49, 137.85, 134.01, 129.34, 129.03, 128.71, 128.28, 127.69, 127.59, 79.70, 77.83, 73.03, 69.30, 65.81, 61.53, 51.41, 49.33, 28.33, 14.04; HRMS (FAB) *m/z* calculated 341.1501 for C₁₉H₂₁N₂O₄ [M+H]⁺, found 341.1493.

D-Form: By applying the same procedure described above, starting with the enantiomer of **1b**, the enantiomer of **4b** was obtained. Yield: 1.7 g (70%). ¹H NMR spectrum was the same as for compound **4b**.

[Benzyloxy-(3-benzylsulfanyl-2-*tert*-butoxycarbonylamino-propionyl)-amino]-acetic acid ethyl ester (4c)

L-Form: By using the same procedure described above, starting with 2 g of **1c**, the desired compound was obtained as colorless viscous oil. Yield: 1.54 g (64%). ¹H NMR (500 MHz, CDCl₃): δ 7.45–9.19 (m, 10H), 5.28 (d, 1H), 5.01 (bs, 1H), 5.00, 4.97 (ABq, *J* = 10.3 Hz, 2H), 4.52, 3.97 (ABq, *J* = 17.5 Hz, 2H), 4.18–4.11 (m, 2H), 3.72, 3.64 (ABq, *J* = 13.1 Hz, 2H), 3.98–3.95 (m, 1H), 3.64–3.60 (m, 1H), 1.47 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (125.76 MHz, CDCl₃): δ 173.69, 167.22, 155.39, 137.90, 133.82, 129.57, 129.19, 128.96, 128.79, 128.39, 126.95, 79.85, 78.09, 61.63, 50.41, 49.27, 36.48, 33.48, 28.36, 14.04; HRMS (FAB) *m/z* calculated 161.0562 for C₃H₉N₂O₄ [M+H]⁺, found 161.0560.

D-Form: By applying the same procedure described above, starting with the enantiomer of **1c**, the enantiomer of

4c was obtained. Yield: 1.57 g (65%). ¹H NMR spectrum was same as for compound **4c**.

1-Benzyloxy-3-benzyloxymethyl-piperazine-2,5-dione (3b)

L-Form: Compound **4b** (1.0 g, 2.1 mmol) was dissolved in 30% TFA in CH₂Cl₂ (20 mL) and stirred for 30 min at RT. The solvent was removed in vacuo and dissolved in MeOH (10 mL) and 5% aqueous KHCO₃ (30 mL) and then stirred for 2 h at RT. The solvent was removed in vacuo and extracted with CH₂Cl₂. The organic layers were dried over MgSO₄ and concentrated in vacuo, then recrystallized in ether to give a white solid. Yield: 0.6 g (87%). ¹H NMR (500 MHz, CDCl₃): δ 8.93 (bs, 1H), 7.33–7.21 (m, 10H), 5.30 (bs, 1H), 4.87 (s, 2H), 4.49, 4.44 (ABq, *J* = 11.5 Hz, 2H), 4.22 (bs, 1H), 3.79–3.78 (m, 1H), 3.50–3.47 (m, 1H), 1.40 (s, 9H); ¹³C NMR (125.76 MHz, CDCl₃): δ 168.15, 155.34, 137.13, 135.02, 129.14, 128.66, 128.49, 128.44, 127.89, 127.70, 80.34, 78.21, 73.38, 69.38, 52.11, 28.21; HRMS (FAB) *m/z* calculated 417.1848 for C₂₂H₂₉N₂O₄S₁ [M+H]⁺, found 417.1857; [α]_D²⁵ = +2.1 (*c* = 0.1 in MeOH).

D-Form: By applying the same procedure described above, starting with the enantiomer of **4b**, the enantiomer of **3b** was obtained. Yield: 0.57 g (80%); [α]_D²⁵ = −1.9 (*c* = 0.1 in MeOH). ¹H NMR spectrum was same as for compound **3b**.

1-Benzyloxy-3-benzylsulfanylmethyl-piperazine-2,5-dione (3c)

L-Form: By using the same procedure described above, starting with 1 g of **4c**, the desired compound was obtained as a white solid. Yield: 0.53 g (75%). ¹H NMR (500 MHz, CDCl₃): δ 9.14 (bs, 1H), 7.38–7.22 (m, 10H), 5.29 (bs, 1H), 4.89 (s, 2H), 4.10 (bs, 1H), 4.49, 4.44 (ABq, *J* = 11.5 Hz, 2H), 2.77–2.67 (m, 2H), 1.42 (s, 9H); ¹³C NMR (125.76 MHz, CDCl₃): δ 168.32, 155.30, 137.72, 134.96, 129.22, 128.95, 128.73, 128.54, 127.20, 80.52, 78.31, 51.69, 36.41, 33.17, 28.23; HRMS (FAB) *m/z* calc'd 503.2216 for C₂₆H₃₅N₂O₆S₁ [M+H]⁺, found 503.2225; [α]_D²⁵ = −7.1 (*c* = 0.1 in MeOH).

D-Form: By applying the same procedure described above, starting with the enantiomer of **4c**, the enantiomer of **3c** was obtained. Yield: 0.55 g (77%); [α]_D²⁵ = +8.4 (*c* = 0.1 in MeOH). ¹H NMR spectrum was same as for compound **3c**.

1-Hydroxy-3-hydroxymethyl-piperazine-2,5-dione (5b)

L-Form: Compound **3b** (200 mg, 0.58 mmol) was stirred in 2 N HCl (0.2 mL) and methanol (10 mL) at room temperature for 30 min with 10% Pd/C (20 mg) under an atmosphere of H₂ balloon. After filtration over celite and concentration under reduced pressure, the product was recrystallized in ether/MeOH to give a white solid. Yield: 88 mg (95%). ¹H-NMR (500 MHz, D₂O): δ 4.34, 4.20 (ABq, *J* = 17.2 Hz, 2H), 4.11 (bs, 1H), 3.89, 3.68 (ABq, *J* = 12.1 Hz, 2H); ¹³C-NMR (125.76 MHz, D₂O): δ 167.37, 163.08, 62.85, 56.69, 52.57; HRMS (FAB) *m/z* calc'd 357.1273 for C₁₉H₂₁N₂O₃S₁ [M+H]⁺, found 357.1293; [α]_D²⁵ = +16.4 (*c* = 0.14 in MeOH).

D-Form: By applying the same procedure described above, starting with the enantiomer of **3b**, the enantiomer of **5b** was obtained. Yield: 83 mg (90%); [α]_D²⁵ = −22.8 (*c* =

0.14 in MeOH). ^1H NMR spectrum was same as for compound **5b**.

1-Hydroxy-3-mercaptopmethyl-piperazine-2,5-dione (**5c**)

L-Form: NH_3 (30 mL) was collected into a solution of **3c** (200 mg, 0.53 mmol) in THF (10 mL) at -78°C . Li (18.4 mg, 2.7 mmol) was added and stirred until a deep blue color was obtained. The reaction mixture was stirred for about 20 min until the deep blue color disappeared and then allowed to warm to RT. N_2 was blown over the solution until it reached dryness. The yellowish-white solid was dissolved in methanolic HCl, evaporated *in vacuo* and then purified by using semi-preparative RP-HPLC with an isocratic elution of 0.1% TFA in H_2O over 15 min to give a white solid. (Flow rate = 3 mL/min, RI-detector, t_{R} = 6.2 min). Yield: 56 mg (60%). ^1H -NMR (500 MHz, D_2O): δ 4.46, 4.27 (ABq, J = 17.2 Hz, 2H), 4.43 (bs, 1H), 3.06 (dd, 1H, J = 2.9 Hz, 14.6 Hz), 2.85 (dd, 1H, J = 3.2 Hz, 14.7 Hz); ^{13}C -NMR (125.76 MHz, D_2O): δ 167.27, 162.87, 55.60, 52.66, 28.88; HRMS (FAB) m/z calc'd 177.0334 for $\text{C}_5\text{H}_9\text{N}_2\text{O}_3\text{S}_1$ [$\text{M}+\text{H}$] $^+$, found 177.0347; $[\alpha]_{\text{D}}^{25}$ = -2.6 (c = 0.19 in MeOH).

D-Form: By applying the same procedure described above, starting with the enantiomer of **3c**, the enantiomer of **5c** was obtained. Yield: >90% by NMR; $[\alpha]_{\text{D}}^{25}$ = 2.4 (c = 0.1 in MeOH). ^1H NMR spectrum was same as for compound **5c**.

Enzyme assay. Inhibition activity was assayed at 37°C in a total volume of 150 mL containing 0.33 mM maltose and 0.03 unit/mL of rice α -glucosidase. After incubation for 15 min, the reaction was stopped by heating at 100°C for 3 min. At this point, 100 mL of glucosidase oxidase/peroxidase (*o*-dianisidin) reagent (Sigma) was added to each tube and the reaction was carried out exactly 30 min at 37°C . After quenching the enzyme reaction by adding 100 mL of 12 N H_2SO_4 , absorbance at 505 nm was measured to determine the amount of D-glucose released. Data interpretation by Grafit 4.0 gave us IC_{50} values to evaluate the concentration needed to inhibit 50% of α -glucosidase activity.

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