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Efficient and stereoselective synthesis of (2*S*,3*S*,4*S*)-3,4-dihydroxyglutamic acid via intramolecular epoxidation

Hyeonjeong Kim [a], Dongwon Yoo [a], Soo Young Choi [b], Young Keun Chung [b], Young Gyu Kim [a,*]

[a] *Department of Chemical and Biological Engineering, Seoul National University, Seoul 151-744, Republic of Korea*
[b] *Department of Chemistry, Seoul National University, Seoul 151-747, Republic of Korea*

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ABSTRACT

The stereoselective synthesis of bioactive (2*S*,3*S*,4*S*)-3,4-dihydroxyglutamic acid hydrochloride salt was achieved. The key step involved an intramolecular nucleophilic epoxidation of homochiral γ-amino-α,β-unsaturated ester **5** containing an *N*-hydroperoxymethyl group followed by regioselective opening of the resulting epoxide with neighboring group participation of the *N*-Boc group. The diastereoselectivity was more than 20:1 by ^{1}H NMR spectroscopy. Thus, (2*S*,3*S*,4*S*)-3,4-dihydroxyglutamic acid hydrochloride salt was prepared from configurationally stable *N*-Boc-D-serinal **4** in 25% overall yield over nine steps.

1. Introduction

L-Glutamic acid acts as an excitatory neurotransmitter in the mammalian central nervous system with selective binding to specific ionotropic or metabotropic glutamate receptors. Each subtype-selective ligand is an important therapeutic target for the treatment of ischemia, epilepsy, and several long-term neurodegenerative syndromes. Various L-glutamic acid analogues have been synthesized, and recently, the intermolecular affinities and selectivities of hydroxylated L-glutamic acids for a particular GluR subclass by hydrogen bonding have stimulated interest in their efficient synthesis. Among these, (2*S*,3*S*,4*S*)-3,4-dihydroxyglutamic acid (DHGA) **1** is known to be an agonist of mGluR1 and a weak antagonist of mGluR4, however, it has no discernible activity with respect to mGluR2[1] (Fig. 1).

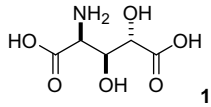
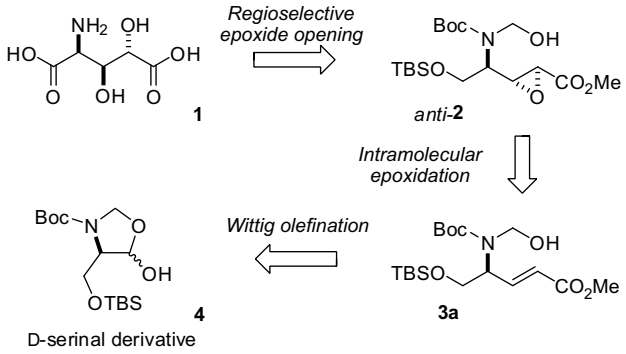


Figure 1. (2*S*,3*S*,4*S*)-3,4-Dihydroxyglutamic acid **1**.

To date, only two research groups have reported the synthesis of (2*S*,3*S*,4*S*)-DHGA.[2] Dodd et al. have completed the first enantiospecific synthesis of the target compound **1** from D-ribose in about 1.1% yield over 17 steps by applying the 2,3-aziridino-γ-lactone methodology.[2a] Oba et al. have synthesized **1** via an enantioselective reduction of the cyclic *meso*-imides that were derived from *meso*-tartaric acid, efficiently but as a minor isomer, together with all of its three stereoisomers.[2b]

We have envisioned that an efficient synthesis for **1** with high stereoselectivity could be achieved by utilizing the *anti*-epoxide intermediate *anti*-**2** obtained from γ-amino-α,β-unsaturated ester **3a** in our previous study for an intramolecular nucleophilic epoxidation (Scheme 1).[3] Stereo- and regioselective opening of the epoxide ring by participation of the neighboring *N*-Boc or hydroxymethyl group would establish the two hydroxyl groups in **1** with the desired stereochemistry.[3,4] The primary alcohol in *anti*-**2** would also provide one of the carboxylic acids in **1**. The small alkyl group, the TBSOCH$_2$– group of γ-amino-α,β-unsaturated ester **3a**, would be favorable to give the resulting epoxide in high stereoselectivity from the intramolecular nucleophilic epoxidation. The intermediate **3a** could be prepared effectively from D-serine as reported.[5] Herein, we report the stereoselective and efficient synthesis of **1**.



Scheme 1. An efficient and stereoselective retrosynthesis for **1**.

* Corresponding author. Tel.: +82 2 880 8347; fax: +82 2 885 6989.
E-mail address: ygkim@snu.ac.kr (Y. G. Kim).

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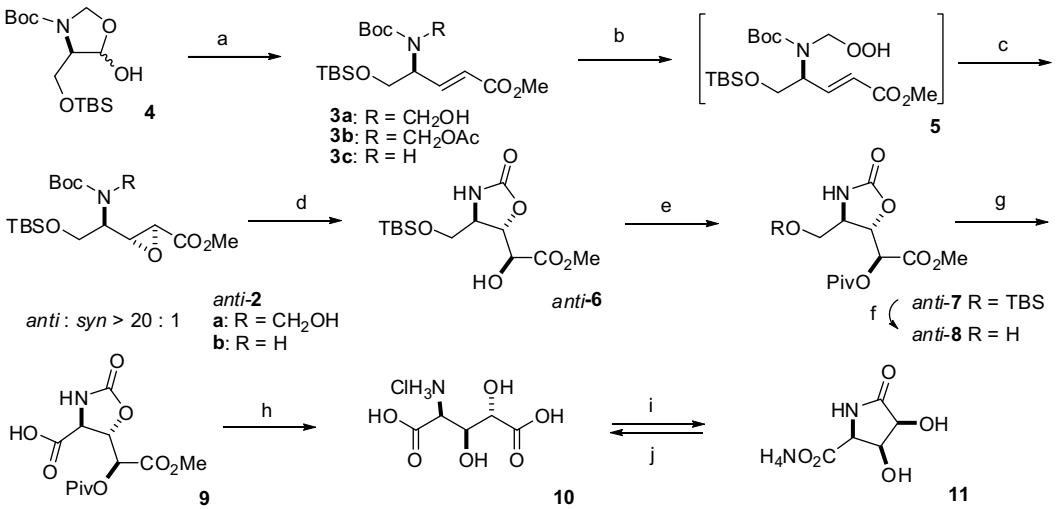
2. Results and discussion

The starting material, an *N*-Boc-D-serinal derivative **4**, was prepared as reported from D-serine in 55% yield over four steps,[5] and the Wittig olefination of **4** was carried out in benzene (Scheme 2). After 2 h of heating under reflux, the required intermediate, (*E*)-γ-amino-α,β-unsaturated ester **3a** with an *N*-hydroxymethyl group, was produced effectively. To facilitate the introduction of the internal hydroperoxy functional group of **5**, the hydroxyl group of **3a** was converted to the acetoxy group with Ac_2O to give (*E*)-γ-amino-α,β-unsaturated ester **3b** with an *N*-acetoxymethyl group in excellent yield. In the presence of *p*-TsOH, **3b** was treated with 30% aqueous H_2O_2 and $MgSO_4$ for 1 h at room temperature to establish the hydroperoxy group of **5** as an internal nucleophile.[6] In contrast to the similar hydroperoxides in the previous report,[3] we could not purify the crude product of **5** because of its instability on silica gel. However, the formation of the desired peroxide intermediate was indicated by comparing the ^{1}H NMR spectrum of crude **5** with that of the corresponding starting materials **3a** and **3b** as well as its different behavior on TLC (R_f and color). Thus, after filtration of $MgSO_4$, a simple treatment of the filtrate with K_2CO_3 in MeOH resulted in the facile intramolecular nucleophilic epoxidation at room temperature within 40 min. As expected, the epoxidation occurred very rapidly because of the intramolecular nature of the reaction. Longer reaction times caused hydrolysis of the ester group into the corresponding acid.

The stereoselectivity for the *anti*-epoxide of **2a** was determined at the stage of **2b** after removal of the hydroxymethyl group in **2a** (PDC oxidation to the formyl group followed by hydrolysis of the formyl group with Cs_2CO_3 in MeOH), because the presence of the hydroxymethyl group made **2a** labile. The selectivity of more than 20 to 1 for the formation of *anti*-**2b** was confirmed by comparing its ^{1}H NMR spectrum with that of the corresponding *syn* epoxide that was produced independently as a major product from an intermolecular *m*-CPBA epoxidation of **3c**. It is known that *syn* epoxides are produced as major products from the *m*-CPBA epoxidation of (*E*)-γ-amino-α,β-unsaturated esters.[7] Although the *anti*-epoxide *anti*-**2a** could be isolated, we went on to the next cyclization step without further purification of the crude product of **2a** because of its instability on silica gel. However, the remaining H_2O_2 and K_2CO_3 in crude **2a** should be quenched with a saturated aqueous Na_2SO_3 solution and an aqueous solution of 1 M HCl at 0 °C. If hydrogen peroxide remained in the organic layer, the yield of the next cyclization reaction became low. The following cyclization reaction with the neighboring group participation required optimization of some of the reaction conditions. When a Lewis acid such as silica gel in MeOH, the conditions successful with other similar epoxides derived from phenylalanine or leucine,[3] was used for the cyclization step of **2a**, the desired oxazolidinone product was produced together with another oxazolidinone product with the *N*-hydroxymethyl group and other impurities. The optimal reaction conditions for **2a** were the cyclization reaction without any Lewis acid in MeOH at 45 °C for 1 day.

Between the two internal nucleophiles, the *N*-Boc group and the hydroxymethyl group, the *N*-Boc group preferentially attacked at the β-position of the *anti*-epoxide with the favored 5-exo cyclization mode[8] to successfully afford the desired *syn*,*anti*-γ-amino-α,β-diol functionality. *trans*-Oxazolidinone **6** with three contiguous stereogenic centers was produced in 62% yield over three steps from **3b**. The *trans* stereochemistry of **6** was suggested by comparing the coupling constants between the protons at C-4 and C-5 ($J_{4,5}$ = 3.8–4.3 Hz) of the oxazolidinone compounds in the ^{1}H NMR spectra. The smaller coupling constant of $J_{4,5}$ in oxazolidinones usually corresponds to a *trans*-relationship between the two protons, while a larger coupling constant than ca. 7 Hz is a good indication of the relative *cis* relationship.[9] The relative relationship among the three stereogenic centers was confirmed by an X-ray structure of the lactam derivative **11** (see below). Although both the major and the minor isomers of **6** had very similar R_f values, we could isolate the pure major isomer *anti*-**6** for characterization, free from the minor isomer, on flash silica gel column chromatography, albeit in a small amount.

The remaining step for obtaining the target compound **1** consists of the transformation of the primary alcohol group of **6** into the desired carboxylic acid group and removal of the protecting groups. Oxazolidinone **6** was treated with Piv_2O to protect the secondary alcohol for 2 days in 86% yield. The selective removal of the TBS protecting group of **7** was accomplished with *p*-TsOH in 2.5 h. The crude product of **8** did not dissolve well in EtOAc and so it was purified by recrystallization in EtOAc. Thus, the minor product in **8** (*syn*-**8**) was removed at the recrystallization step to give only the major product, *anti*-**8**, as white crystals in 88% yield. For the formation of carboxylic acid, various oxidants such as RuO_4, TPAP, TEMPO, PDC, Jones reagent, and CrO_3 were tried, but only the reaction



Scheme 2. Reagents and conditions: (a) $Ph_3P{=}CHCO_2Me$, PhH, reflux, 2 h, 96% (**3a**); Ac_2O, TEA, DMAP, CH_2Cl_2, 30 min, 98% (**3b**); (b) aq H_2O_2, $MgSO_4$, *p*-TsOH, DME, 1 h; (c) K_2CO_3, MeOH, 40 min; (d) MeOH, 45 °C, 1 d, 62% (three steps); (e) Piv_2O, TEA, DMAP, CH_2Cl_2, 2 d, 86%; (f) *p*-TsOH, MeOH, 2.5 h, 88%; (g) CrO_3, H_5IO_6, CH_3CN, 99%; (h) 6 N aq HCl, reflux, 16 h, 58%; (i) NH_4OH, 7 d, crystallization or cation exchange resin column (DOWEX® 50W × 4); (j) 6 N aq HCl, 80 °C, 4 h, quant.

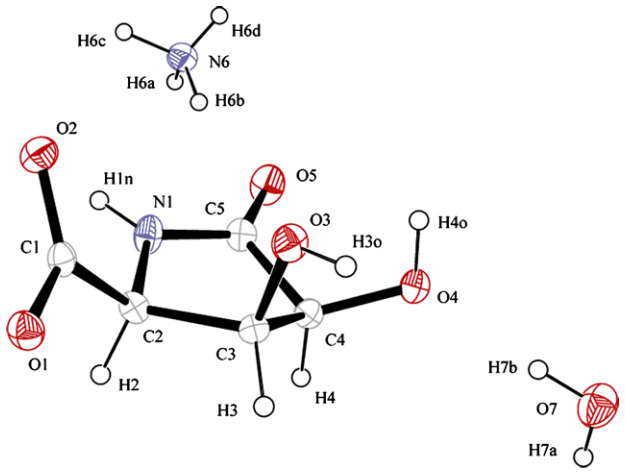


Figure 2. ORTEP drawing of **11**.

with CrO_3 successfully oxidized the primary alcohol group of **8**-*anti* into the carboxylic acid of **9** in 99%.[10] The crude product of **9** was not purified further because its ^{1}H NMR spectrum was clean enough. An acidic hydrolysis of crude **9** in an aqueous solution of 6 M HCl produced the target compound **1** as its hydrochloride salt **10**, (2*S*,3*S*,4*S*)-3,4-dihydroxyglutamic acid hydrochloride salt. Production of succinic acid was always accompanied as a side reaction under vigorous hydrolytic conditions, probably because of the decomposition of the deprotected product, free dihydroxyglutamic acid **1**. The side product of the acidic hydrolysis was removed by rinsing the crude salt with hot acetonitrile. When the hydrolysis reaction was carried out at lower temperatures, such as 80 °C, it was not successful at all. Finally, (2*S*,3*S*,4*S*)-dihydroxyglutamic acid was obtained as its hydrochloride salt **10** in 58% yield from **9**.

In an effort to obtain the purified product of **1** with an ion exchange resin, an aqueous solution of the crude off-white hydrochloride salt from the acidic hydrolysis of **9** was passed through a cation exchange resin column (DOWEX® 50W × 4), and the hydrolysis product on the resin column was eluted with an aqueous ammonia solution to give its ammonium salt. After vacuum evaporation of the eluted aqueous ammonia solution, the resulting ammonium salt was recrystallized in EtOH/H_2O (1.5/1, v/v) to give white solid in 20% overall yield from **9**. A slow process of further recrystallization of the resulting white solid in water afforded cube-shaped single crystals, X-ray structure of which showed that they had the lactam structure as shown in Figure 2.[11] It should be noted that the eluted ammonium salt of the hydrolysis product did cyclize into lactam **11**. The X-ray structure of **11** is also an unambiguous proof for the relative configuration at the three stereogenic centers of 3,4-dihydroxyglutamic acid to be (2*S*,3*S*,4*S*) that were established in the present study. The ammonium salt of lactam **11** was hydrolyzed with an aqueous solution of 6 M HCl at 80 °C for 4 h to give back **10** quantitatively, which was identical to that obtained from the acidic hydrolysis of **9**.

3. Conclusion

We have prepared (2*S*,3*S*,4*S*)-3,4-dihydroxyglutamic acid hydrochloride salt **10** in 25% yield over nine steps from *N*-Boc-D-serinal derivative **4** with high stereoselectivity. The two new hydroxyl groups were introduced stereoselectively via an intramolecular nucleophilic epoxidation followed by a regioselective opening of the epoxide ring by participation of the neighboring *N*-Boc carbamate group. The stereoselectivity of the epoxidation was more than 20:1 as determined by ^{1}H NMR measurement.

4. Experimental

Materials were obtained from commercial suppliers and used without further purification. Air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere using oven-dried glassware and standard syringe/septa techniques. The reactions were monitored with a SiO_2 TLC plate under UV light (254 nm), followed by visualization with a ninhydrin staining solution. Column chromatography was performed on Silica Gel 60 (70–230 mesh). Optical rotations were determined with a digital polarimeter and are the average of 10 measurements. ^{1}H and ^{13}C NMR spectra were measured at 300 MHz and 75 MHz, respectively, in $CDCl_3$ unless stated otherwise and data were reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, integration, coupling constant in Hertz).

4.1. Methyl (2*E*,4*S*)-4-[(*N*-*tert*-butoxycarbonyl)-(*N*-hydroxymethyl)]amino-5-(*tert*-butyldimethylsilyloxy)pent-2-enoate 3a

To a solution of **4** (1.751 g, 5.25 mmol) in benzene (100 mL) was added methyl (triphenylphosphoranylidene) acetate (2.107 g, 6.30 mmol). The mixture was heated under reflux for 2.5 h, and then concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (8:1 hexane/EtOAc) to give (*E*)-olefin **3a** (1.963 g, 96%) as a colorless oil. $[\alpha]_D^{19} = -3.0$ (*c* 0.11, $CHCl_3$); $R_f = 0.36$ (2:1 hexane/EtOAc); IR (film on a silicon wafer) 3518, 2963, 2860, 1728, 1704, 1680, 1109 cm^{-1}; ^{1}H NMR δ 0.11 (s, 6H), 0.90 (s, 9 H), 1.49 (s, 9H), 3.45–3.65 (m, 1H), 3.76 (s, 3H), 3.87 (m, 2H), 4.51–4.94 (m, 1H), 4.62 (br s, 1H), 4.90 (br s, 1H), 5.96 (d, 1H, *J* = 16.0), 6.95 (dd, 1H, *J* = 16.0, 4.9); ^{13}C NMR δ −5.3, 18.4, 25.9, 28.5, 51.9, 58.6, 63.8, 70.0, 81.4, 122.7, 144.8, 156.7, 166.6; HRMS (CI) calcd for $C_{18}H_{36}NO_6Si$ 390.2312 ([M+H]$^+$), found 390.2307.

4.2. Methyl (2*E*,4*S*)-4-[(*N*-acetoxymethyl)-(*N*-*tert*-butoxycarbonyl)]amino-5-(*tert*-butyldimethylsilyloxy)pent-2-enoate 3b

To a solution of (*E*)-olefin **3a** (547 mg, 1.40 mmol) in CH_2Cl_2 (30 mL) was added Ac_2O (286 mg, 2.80 mmol), TEA (283 mg, 2.80 mmol), and DMAP (17.1 mg, 0.140 mmol). The mixture was stirred for 30 min, and then partitioned between H_2O (2 × 20 mL) and CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (4:1 hexane/EtOAc) to give **3b** (597 mg, 99%) as colorless oil. $[\alpha]_D^{19} = +4.8$ (*c* 0.50, $CHCl_3$); $R_f = 0.50$ (2:1 hexane/EtOAc); IR (film on a silicon wafer) 2971, 2880, 1730, 1711, 1701, 1157 cm^{-1}; ^{1}H NMR δ 0.06 (s, 6H), 0.88 (s, 9H), 1.47 (s, 9H), 2.05 (s, 3H), 3.75 (s, 3H), 3.78–3.99 (m, 2H), 4.47–4.68 (m, 1H), 5.30 (br s, 1H), 5.41 (br s, 1H), 5.94 (d, 1H, *J* = 15.8), 6.96 (dd, 1H, *J* = 15.8, 4.6); ^{13}C NMR δ −5.4, 18.2, 21.2, 25.9, 28.4, 51.8, 59.6, 63.2, 71.9, 81.6, 122.3, 144.8, 154.3, 166.6, 170.6; HRMS (CI) calcd for $C_{20}H_{38}NO_7Si$ 430.2261 ([M–H]$^+$), found 430.2264.

4.3. Methyl (2*S*,4′*R*,5′*S*)-[4′-(*tert*-butyldimethylsilyloxymethyl)oxazolidin-2′-on-5′-yl]-2-hydroxyacetate *anti*-6

To a solution of **3b** (470 mg, 1.09 mmol) in dimethoxyethane (23 mL) were added an aqueous solution of 30% H_2O_2 (0.78 mL, 7.63 mmol), *p*-TsOH (62.8 mg, 0.33 mmol), and $MgSO_4$ (1.00 g) [$MgSO_4$ was added to reduce the side reaction by H_2O present in aqueous 30% H_2O_2 and *p*-TsOH to facilitate the substitution reaction of the acetoxy group with H_2O_2]. The reaction mixture was stirred for 1 h at room temperature. After filtration, K_2CO_3

(452 mg, 3.27 mmol) and MeOH (8.4 mL) were added to the filtrate. The reaction was completed within 40 min. After diluting the reaction mixture with Et_2O (20 mL), saturated aq Na_2SO_3 (2 mL) and 1 M aq HCl solutions were added dropwise at 0 °C, and the resulting mixture was partitioned. The aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **2a**. The crude epoxide product **2a** in methanol (50 mL) was stirred at 45 °C for 1 day. The resulting mixture was concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (2:1 hexane/EtOAc) to give **6** (215 mg, 62%) as a colorless viscous oil. *anti*-**6**: $[\alpha]_D^{19} = +38.8$ (*c* 1.00, $CHCl_3$); R_f = 0.10 (1:1 hexane/EtOAc); IR (film on a silicon wafer) 3518, 3747, 2890, 1746, 1719, 1006 cm^{-1}; ^1H NMR δ 0.06 (s, 6H), 0.88 (s, 9H), 3.55 (dd, 1H, *J* = 10.5, 4.8), 3.63 (dd, 1H, *J* = 10.5, 5.3), 3.80 (s, 3H), 3.89 (m, 1H), 4.48 (d, 1H, *J* = 5.1), 4.58 (dd, 1H, *J* = 5.1, 3.0), 4.66 (dd, 1H, *J* = 4.1, 3.0), 6.36 (s, 1H); ^{13}C NMR δ −5.3, 18.4, 26.0, 53.0, 54.4, 64.6, 71.7, 79.2, 159.6, 171.1; HRMS (CI) calcd for $C_{13}H_{26}NO_6Si$ 320.1529 ($[M+H]^+$), found 320.1529.

4.4. Methyl (2*S*,4′*R*,5′*S*)-[4′-(*tert*-butyldimethylsilyloxy)-methyloxazolidin-2′-on-5′-yl]-2-trimethylacetoxyacetate *anti*-7

To a solution of **6** (555 mg, 1.74 mmol) in CH_2Cl_2 (5 mL) were added Piv_2O (0.64 mL, 3.38 mmol), TEA (0.47 mL, 3.38 mmol), and DMAP (20.6 mg, 0.169 mmol). The mixture was stirred for 2 days and then partitioned between H_2O (2 × 20 mL) and CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (4:1 hexane/EtOAc) to give **7** (604 mg, 86%) as white solid. *anti*-**7**: mp 103 °C; $[\alpha]_D^{18} = +34.7$ (*c* 0.30, $CHCl_3$); R_f = 0.65 (1:1 hexane/EtOAc); IR (film on a silicon wafer) 3297, 2965, 1772, 1737, 1142 cm^{-1}; ^1H NMR δ 0.07 (s, 6H), 0.89 (s, 9H), 1.26 (s, 9H), 3.55 (dd, 1H, *J* = 10.3, 5.5), 3.58 (dd, 1H, *J* = 10.3, 5.2), 3.78 (s, 3H), 3.93 (m, 1H), 4.76 (dd, 1H, *J* = 3.8, 2.9), 5.36 (d, 1H, *J* = 2.9), 5.84 (s, 1H); ^{13}C NMR δ −5.4, 18.3, 25.9, 27.0, 38.9, 53.0, 54.7, 64.3, 72.2, 76.4, 159.1, 166.9, 177.3; HRMS (CI) calcd for $C_{18}H_{34}NO_7Si$ 404.2105 ($[M+H]^+$), found 404.2107.

4.5. Methyl (2*S*,4′*R*,5′*S*)-[4′-(hydroxymethyl)oxazolidin-2′-on-5′-yl]-2-trimethylacetoxyacetate *anti*-8

To a solution of **7** (725 mg, 1.80 mmol) in MeOH (7 mL) was added *p*-TsOH (342.4 mg, 1.80 mmol). The mixture was stirred for 3 h. The mixture was extracted with EtOAc (2 × 10 mL) and brine (2 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by recrystallization in EtOAc to give *anti*-**8** (457 mg, 88%) as white crystals. mp 186 °C; $[\alpha]_D^{19} = +36.2$ (*c* 0.10, acetone); R_f = 0.23 (1:4 hexane/EtOAc); IR (film on a silicon wafer) 3743, 3383, 2967, 2881, 1753, 1713, 1688 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.23 (s, 9H), 3.58 (ddd, 2H, *J* = 15.7, 10.8, 4.9), 3.76 (s, 3H), 3.92 (m, 1H), 4.32 (t, 1H, *J* = 5.6), 4.83 (dd, 1H, *J* = 4.3, 3.0), 5.32 (d, 1H, *J* = 3.0), 6.89 (s, 1H); ^{13}C NMR (acetone-d_6) δ 27.1, 39.3, 53.0, 55.2, 64.0, 73.2, 76.8, 158.4, 167.6, 177.4; HRMS (CI) calcd for $C_{12}H_{20}NO_7$ 290.1240 ($[M+H]^+$), found 290.1241.

4.6. (1″*S*,4′*S*,5′*S*)-[5′-(1″-Methoxycarbonyl-1″-trimethylacetoxy)-methyloxazolidin-2′-on-4′-yl]formic acid 9

To a solution of periodic acid (1.400 g, 6.14 mmol) in MeCN (10 mL) was added chromium trioxide (26.8 mg, 0.268 mmol) at 0 °C. A solution of *anti*-**8** (775 mg, 2.68 mmol) in MeCN (10 mL) was added slowly. The mixture was stirred for 30 min. *i*-PrOH was used to quench the excess oxidant. The mixture was concentrated under reduced pressure and the residue was partitioned with EtOAc (2 × 10 mL) and H_2O (2 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford **9** (803 mg, 99%) as white solid. mp 68 °C; $[\alpha]_D^{20} = +36.0$ (*c* 0.10, acetone); R_f = 0.11 (85:15:3 $CHCl_3$/MeOH/AcOH); IR (film on a silicon wafer) 3743, 3518, 3300, 1746 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.22 (s, 9H), 3.76 (s, 3H), 4.48 (dd, 1H, *J* = 4.3, 1.5), 5.10 (dd, 1H, *J* = 4.3, 2.9), 5.35 (d, 1H, *J* = 2.9), 7.46 (s, 1H); ^{13}C NMR (acetone-d_6) δ 26.2, 38.4, 52.3, 54.0, 71.9, 75.9, 157.0, 170.6, 176.4; HRMS (CI) calcd for $C_{12}H_{18}NO_8$ 304.1032 ($[M+H]^+$), found 304.1031.

4.7. (2*S*,3*S*,4*S*)-4-Amino-2,3-dihydroxypentanedioic acid hydrochloride 10

The crude acid **9** (520 mg, 1.71 mmol) was hydrolyzed by heating under reflux in 6 M aq HCl (15 mL) for 16 h, and the resulting mixture was concentrated under reduced pressure. The residue was rinsed with hot acetonitrile to remove impurities, yielding **10** (214 mg, 58%) as an off-white solid, which was too hygroscopic for its melting point to be measured. $[\alpha]_D^{20} = +7.7$ (*c* 0.30, H_2O); IR (KBr) 3870, 1633, 1473, 1460, 1398, 1077 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 4.30 (d, 1H, *J* = 3.0), 4.54 (d, 1H, *J* = 4.8), 4.61 (dd, 1H, *J* = 4.8, 3.0); ^{13}C NMR (100 MHz, D_2O) δ 54.7, 69.2, 72.8, 170.5, 174.6; HRMS (FAB) calcd for $C_5H_{11}ClNO_6$ 216.0275 ($[M+H]^+$), found 216.0272.

4.8. Ammonium (3′*S*,4′*S*,5′*S*)-(3′,4′-dihydroxypyrrolidin-2′-one)-5′-ylformate 11

The crude acid **9** (449 mg, 1.48 mmol) was hydrolyzed by heating under reflux in 6 M aq HCl (10 mL) for 16 h, and the resulting mixture was concentrated under reduced pressure. The residue was purified with ion exchange column chromatography on DOWEX® 50W × 4 to give **11** (106 mg, 0.540 mmol, eluted with an aqueous ammonia solution). It was purified again by recrystallization in EtOH and H_2O (1.5:1 v/v) to afford **11** (57 mg, 0.291 mmol) as white crystal. mp 214 °C (decomp.); $[\alpha]_D^{19} = -77.0$ (*c* 0.10, H_2O); IR (KBr) 3219, 2943, 1720, 1675, 1578, 1420, 1318, 1227, 1130 cm^{-1}; ^1H NMR (500 MHz, D_2O) 4.21 (d, 1H, *J* = 3.9), 4.45 (d, 1H, *J* = 4.9), 4.63 (apparently t, 1H, *J* = 4.4); ^{13}C NMR (D_2O) δ 60.7, 71.0, 72.1, 175.3, 177.6; HRMS (FAB) calcd for $C_5H_{11}N_2O_5$ 179.0668 ($[M+H]^+$), found 179.0668.

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11. X-ray analysis. Single-crystal diffraction data were measured by an Enraf-Nonius CCD single-crystal X-ray diffractometer at room temperature using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Preliminary orientation matrices and unit cell parameters were obtained from the peaks of the first 10 frames, and then refined using the whole data set. Frames were integrated and corrected for Lorentz and polarization effects using DENZO. The structure was solved by direct methods using SHELXS-97 and refined by full-matrix least-squares with SHELXL-97. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were found during refinement. Crystal data for **11**: $C_5H_{10}N_2O_5{\cdot}H_2O$ (295 K). $M = 196.17$, monoclinic, space group $P2_{1/n}$, $a = 9.6982(5)$ Å, $b = 6.2010(4)$ Å, $c = 14.7620(6)$ Å, $\beta = 97.283(3)^\circ$, $V = 880.60(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.480$ g/cm^{-3}, absorption coefficient = 0.136 mm^{-1}, total reflections collected 3416, unique 1998 ($R_{int} = 0.0150$), GOF = 1.071, $R_1 = 0.0342$, $R_w = 0.0922$ ($I > 2\sigma(I)$). The data of **11** can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The CCDC number is 695661.