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A concise approach to homochiral 3,4-dihydroxyglutamic acids

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Abstract—A concise diastereoselective synthesis of 3,4-dihydroxyglutamic acids was investigated. The key reaction in this synthesis is stereoselective cyanation of an optically active *N*-acyliminium intermediate derived from L- or D-tartaric acid. The stereoselectivity in the cyanation reaction could be controlled by the protective group of the hydroxyl function. Deprotection of the obtained cyanolactam followed by acidic hydrolysis afforded the desired 3,4-dihydroxyglutamic acids. The 3,4-dihydroxyglutamic acids obtained in this synthesis are (2*S*,3*S*,4*R*)-, (2*R*,3*S*,4*R*)-, (2*S*,3*R*,4*S*)-, and (2*R*,3*R*,4*S*)-isomers and the three latter compounds are novel derivatives of glutamic acids.

1. Introduction

Because of the implication of glutamate receptors in brain ischemia, epilepsy, and neurodegenerative syndromes such as Alzheimer's, Parkinson's, and Huntington's diseases,[1] a large number of analogues of glutamic acid have been prepared to probe the physiological role of the receptors.[2] Most of the reported glutamic acid analogues are alkyl substituted derivatives including conformationally restricted cyclic or bicyclic compounds and some of them exhibit potent affinity to specific glutamate receptors and are expected to have therapeutic applications.

On the other hand, hydroxylated glutamic acid derivatives are less studied despite the potential of the high-affinity ligands based on their additional ability of intra- and intermolecular hydrogen bonding. 3,4-Dihydroxyglutamic acid is a naturally occurring amino acid, which was isolated for the first time from the seeds of *Lepidum sativum* and the leaves of *Rheum rhaponticum* over 40 years ago;[3] however, the relative and absolute configurations of the three chiral centers are unknown. Although some reports on the preparation of 3- and 4-hydroxyglutamic acids have been published,[4] only two methods for the preparation of enantiopure (2*S*,3*S*,4*S*)[5] and (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acids[6] have appeared in the literature, and the former compound was found to be a selective agonist of mGluR1. However, the methods require multistep synthesis from the commercially available starting material and lack applicability to other diastereomers. Therefore, we set out to devise a simple and general approach to all diastereomers.

In our preliminary communication,[7] we reported a concise diastereoselective synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid, in which L-tartaric acid was adopted as the starting material because the acid already contains the required two hydroxyl groups with established configurations. We here disclose a concise approach to (2*S*,3*R*,4*S*)-3,4-dihydroxyglutamic acid as well as the (2*S*,3*S*,4*R*)-isomer. In this synthesis, the corresponding (2*R*,3*R*,4*S*) and (2*R*,3*S*,4*R*)-isomers were also obtained as concomitant products.

2. Results and discussion

The optically active cyclic imides[8] **1a** and **1b** derived from L-tartaric acid were converted to acetoxylactams **2a** and **2b** by reduction with sodium borohydride followed by acetylation (Scheme 1). The acetylation of the incipient hydroxylactams was necessary for the subsequent cyanation reaction. Table 1 shows the representative results of stereoselective cyanation of the acetoxylactams **2a** and **2b**. When a solution of lactam **2a** and tributyltin cyanide[9] (1.5 equiv.) in toluene was treated with trifluoroborane etherate (2 equiv.) at room temperature, a 90:10 mixture of the desired cyanolactams[10] **4a** and **5a** was obtained in 94% yield (entry 4). The choice of tributyltin cyanide over trimethylsilyl cyanide and toluene over dichloromethane as the solvent proved to be advantageous for the stereoselective cyanation of lactam **2a** (entries 1–4). Other Lewis acids or lower reaction temperature did not improve the selectivity. The stereochemistry of cyanolactams **4a** and **5a** was assigned according to the observed vicinal coupling constants $J_{4,5}$=6.7 and 4.4 Hz, respectively. In similar systems,[11–13] the *cis* coupling constant is usually larger than that of the *trans* isomer. Final confirmation of the

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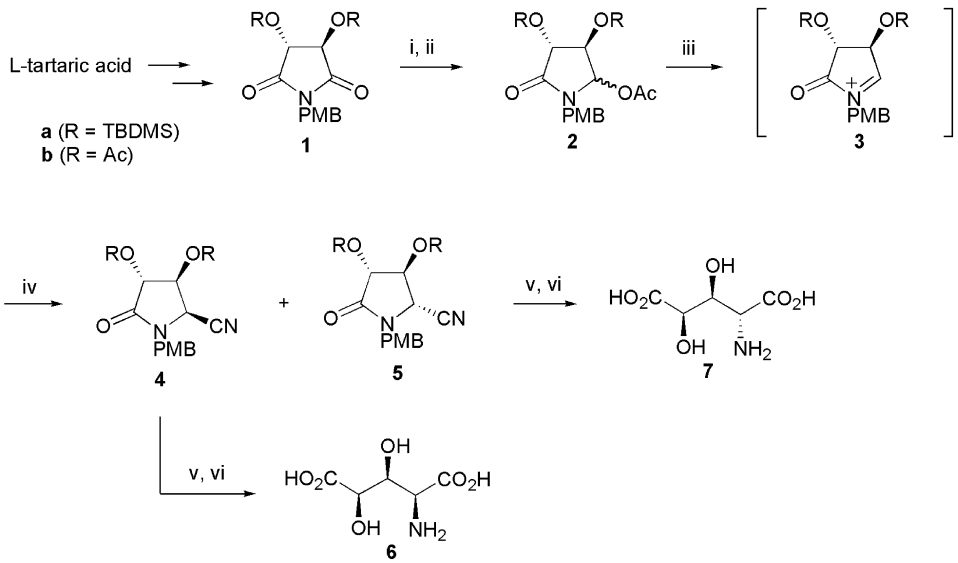


Scheme 1. (i) $NaBH_4$; (ii) Ac_2O in pyridine; (iii) BF_3-OEt_2; (iv) Me_3SiCN or Bu_3SnCN; (v) $Ce(NH_4)_2(NO_2)_6$; (vi) 6 M HCl, 110°C, then Dowex 50W-W8.

stereochemistry was provided by transformation into 3,4-dihydroxyglutamic acids **6** and **7** (vide infra).

There are some reports on the Lewis acid-promoted addition of tin and silicon nucleophiles to the *N*-acyliminium ion syn to the adjacent *O*-TBDMS group,[12–14] revealing that this stereochemical outcome is not ruled by steric effects. Although the actual cause of this unexpected stereoselectivity has not been established, Cieplak-type stereoelectronic effect[15] or the exterior frontier orbital extension model (EFOE model)[16] may be necessary to explain the observed facial diastereoselection.

On the other hand, the stereoselectivity in the cyanation reaction of acetoxylactam **2b**, in which the *O*-protective group is an acetyl group, is completely reversed, affording an 18:82 mixture of cyanolactams **4b** and **5b** in 80% yield (entry 5). The predominant formation of **5b** can be attributed to the normal steric effect between the cyanating reagent and the neighboring acetoxy group. The use of toluene as the solvent (entry 6) or tributyltin cyanide as the cyanating reagent gave no improvement in this case.

These results indicate that the face-selectivity of the nucleophilic cyanation toward the *N*-acyliminium intermediate **3** can be controlled by the *O*-protective group. Thaning and Wistrand reported similar stereocontrolled reaction with 3 or 4-substituted *N*-acylpyrrolidinium ions.[13]

Table 1. Stereoselective cyanation of optically active acetoxylactam **2**

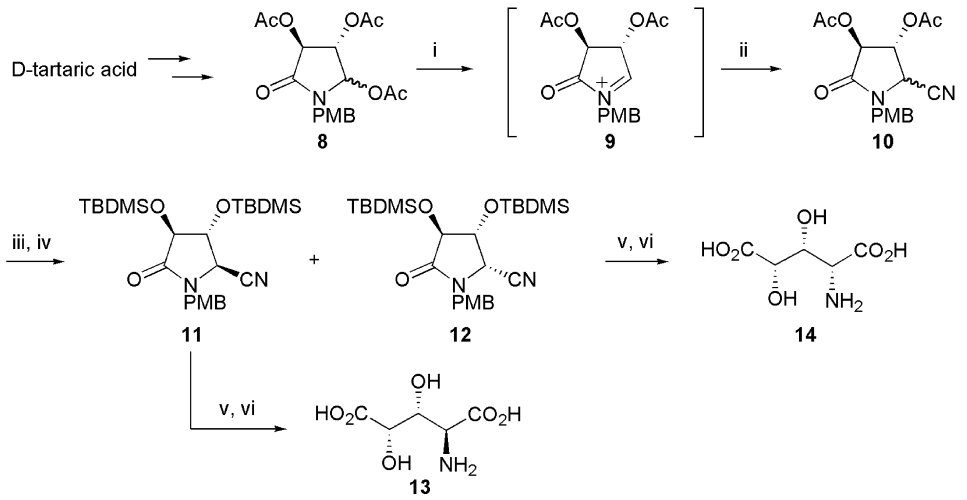
Entry	Acetoxy-lactam	Metal cyanide	Solvent	Selectivity (**4**/**5**)[a]	Yield (%)
1	**2a**	Me_3SiCN	CH_2Cl_2	80/20	94
2	**2a**	Me_3SiCN	Toluene	84/16	96
3	**2a**	Bu_3SnCN	CH_2Cl_2	89/11	98
4	**2a**	Bu_3SnCN	Toluene	90/10	94
5	**2b**	Me_3SiCN	CH_2Cl_2	18/82	80
6	**2b**	Me_3SiCN	Toluene	23/77	82

[a] Determined by ^1H NMR spectroscopy.

The diastereomeric cyanolactams **4** and **5** can be easily separated by flash column chromatography on silica gel when the *O*-protective group is a TBDMS group. The major isomer **4a** was then treated with diammonium cerium nitrate to remove the *N*-PMB protecting group followed by 6 M HCl at 110°C. The crude product was purified by ion exchange column chromatography (Dowex 50W-X8) to furnish (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid (**6**)[6] in 73% yield based on **4a**. The conversion of the minor isomer **5a** was also carried out and the diastereomeric (2*R*,3*S*,4*R*)-3,4-dihydroxyglutamic acid (**7**), a novel glutamic acid derivative, was obtained in 58% yield.

In order to obtain the corresponding (2*S*,3*R*,4*S*)-isomer, the enantiomer of 3,4-dihydroxyglutamic acid **7**, as a major product, we next carried out the stereoselective cyanation of triacetate **8** derived from D-tartaric acid (Scheme 2). Treatment of acetoxylactam **8** with trimethylsilyl cyanide in the presence of trifluoroborane etherate gave cyanolactam **10** in 93% yield as an 80:20 mixture of diastereomers. This diastereomeric mixture was difficult to separate completely by column chromatography so the *O*-protective group was once transformed into a TBDMS group. After chromatographic separation, diastereomers **11** and **12**, obtained in 53 and 22% yields, respectively, were independently treated with diammonium cerium nitrate followed by acidic hydrolysis to afford novel (2*S*,3*R*,4*S*) and (2*R*,3*R*,4*S*)-3,4-dihydroxyglutamic acids (**13**) and (**14**) in 40 and 35% yields, respectively.

In summary, we have demonstrated a concise diastereoselective synthesis of 3,4-dihydroxyglutamic acids based on the stereoselective cyanation of the chiral *N*-acyliminium ion derived from L- or D-tartaric acid. It was found that the stereoselectivity in the cyanation reaction could be controlled by the *O*-protective group. From *O*-TBDMS acetoxylactam **2a** derived from L-tartaric acid, (2*S*,3*S*,4*R*)-3,4-dihydroxyglutamic acid (**6**) was obtained as a major product, whereas the cyanation of *O*-acetyl lactam **8** derived from D-tartaric acid led mainly to the corresponding (2*S*,3*R*,4*S*)-isomer **13**. Since the minor cyanolactams **5a**



Scheme 2. (i) BF_3-OEt_2; (ii) Me_3SiCN; (iii) AcCl, EtOH; (iv) TBDMS–Cl, imidazole; (v) $Ce(NH_4)_2(NO_2)_6$; (vi) 6 M HCl, 110°C, then Dowex 50W-X8.

and **12** could be easily isolated from the reaction mixture, the diastereomeric (2*R*,3*S*,4*R*)- and (2*R*,3*R*,4*S*)-3,4-dihydroxyglutamic acids **7** and **14** were also obtained in an enatiomerically pure form. Among them, the amino acids **7**, **13**, and **14** are novel derivatives of hydroxyglutamic acids.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. All chemical shifts are reported as δ values (ppm) relative to residual chloroform (δ_H 7.26), sodium 3-(trimethylsilyl)[2,2,3,3-D_4]propionate (δ_H 0.00 and δ_c 0.00), or the central peak of $CDCl_3$ (δ_c 77.00). High-resolution mass spectra (HRMS) were determined using perfluorokerosene as an internal standard. Optical rotations were measured on a HORIBA SEPA-200 polarimeter.

3.1.1. (3*R*,4*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-5-acetoxy-1-(4-methoxybenzyl)-2-pyrrolidinone (2a). To a solution of imide **1a** (14.4 g, 30.0 mmol) in methanol (300 mL) was added sodium borohydride (5.67 g, 150 mmol) at 0°C. After it was stirred for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and evaporated to dryness to give a hydroxylactam as a white solid. To a solution of the hydroxylactam in pyridine (50 mL) was added acetic anhydride (15.3 g, 150 mmol), and the reaction mixture was stirred at room temperature overnight. After evaporation of the solvent, the residue was extracted with chloroform. The organic layer was washed successively with 1 M HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate=50:50) to give the title compounds **2a** (14.0 g, 89%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 0.01 (s, 3H), 0.06 (s, 3H), 0.14 (s, 3H), 0.19 (s, 3H), 0.81 (s, 9H), 0.91 (s, 9H), 1.90 (s, 3H), 3.75 (s, 3H), 3.96 (dd, *J*=3, 2 Hz, 1H), 4.02 (d, *J*=3 Hz, 1H), 4.15 (d, *J*=15 Hz, 1H), 4.61 (d, *J*=15 Hz, 1H), 5.74 (d, *J*=2 Hz, 1H), 6.80 (d, *J*=9 Hz, 2H), 7.14 (d, *J*=9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ −5.19, −5.15, −5.06, −4.57, 17.57, 17.96, 20.52, 25.35, 25.52, 43.63, 55.00, 76.58, 77.10, 86.62, 113.77, 128.06, 129.12, 158.93, 170.09, 172.27. MS (CI) *m/z* 524 (MH^+). HRMS (EI, 70 eV) *m/z* 508.2519 [$(M-Me)^+$, calcd for $C_{25}H_{42}NO_6Si_2$ 508.2551].

3.1.2. (3*R*,4*S*,5*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-5-cyano-1-(4-methoxybenzyl)-2-pyrrolidinone (4a) and (3*R*,4*S*,5*S*)-3,4-bis[(*tert*-butyldimethylsilyl)oxy]-5-cyano-1-(4-methoxybenzyl)-2-pyrrolidinone (5a). To a solution of acetoxylactam **2a** (520 mg, 1.00 mmol) and tributyltin cyanide (480 mg, 1.50 mmol) in toluene (20 mL) was added a solution of boron trifluoride etherate (280 mg, 2.00 mmol) in toluene (1 mL) at 0°C under an argon atmosphere, and the reaction mixture was stirred for 5 min. After it was stirred at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous Na_2CO_3 and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate=50:50) to give the title compound **5a** (50.0 mg, 10%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.16 (s, 3H), 0.21 (s, 3H), 0.84 (s, 9H), 0.93 (s, 9H), 3.75 (d, *J*=4 Hz, 1H), 3.78 (s, 3H), 3.91 (d, *J*=15 Hz, 1H), 4.06 (d, *J*=4 Hz, 1H), 4.32 (dd, *J*=4, 4 Hz, 1H), 5.14 (d, *J*=15 Hz, 1H), 6.86 (d, *J*=9 Hz, 2H), 7.18 (d, *J*=9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ −5.02, −4.79 (2C), −4.41, 17.58, 18.02, 25.42, 25.56, 44.40, 52.38, 55.15, 76.48, 76.68, 114.32, 115.50, 126.15, 129.75, 159.51, 170.38. MS (CI) *m/z* 491 (MH^+). HRMS (EI, 30 eV) *m/z* 475.2455 [$(M-Me)^+$, calcd for $C_{24}H_{39}N_2O_4Si_2$ 475.2448].

Further elution with a mixture of hexane and ethyl acetate (50:50) gave the corresponding (3*R*,4*S*,5*R*)-isomer **4a** (430 mg, 88%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.11 (s, 3H), 0.17 (s, 3H), 0.23 (s, 3H), 0.91 (s, 9H), 0.93 (s, 9H), 3.80 (s, 3H), 3.96 (d, *J*=15 Hz, 1H), 4.09 (d, *J*=7 Hz, 1H), 4.14 (dd, *J*=7, 7 Hz, 1H), 4.31 (d, *J*=7 Hz, 1H), 4.99 (d, *J*=15 Hz, 1H), 6.88 (d, *J*=9 Hz, 2H), 7.19 (d, *J*=9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ −4.99, −4.90, −4.85, −4.40, 17.74, 18.15, 25.50, 25.59, 44.94, 50.64, 55.20, 73.40, 75.77, 114.38, 114.51, 125.75, 129.91, 159.65,

170.42. MS (CI) *m/z* 491 (MH^+). HRMS (EI, 30 eV) *m/z* 475.2491 [$(M-Me)^+$, calcd for $C_{24}H_{39}N_2O_4Si_2$ 475.2448].

3.1.3. (2*S*,3*S*,4*R*)-3,4-Dihydroxyglutamic acid (6). To a suspension of cyanolactam **4a** (4.80 g, 11.0 mmol) and diammonium cerium (IV) nitrate (12.0 g, 22.0 mmol) in acetonitrile (33 mL) was added water (11 mL) at room temperature, and the resulting mixture was stirred for 4 h. The reaction mixture was then diluted with ethyl acetate, washed with water, and dried over $MgSO_4$. After removal of the solvent, the residue was hydrolyzed in refluxing 6 M HCl (300 mL) overnight. The cooled aqueous solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion exchange column chromatography on Dowex 50W-X8 to furnish the title compound **6** (1.43 g, 73%) as white powder, $[\alpha]_D^{25}=+8.59$ (*c* 1.08, 18% HCl) (lit,[6] $[\alpha]_D^{28}=+8.5$ (*c* 1.08, 18% HCl)). ^1H NMR (D_2O) δ 3.96 (d, *J*=3 Hz, 1H), 4.24 (d, *J*=2 Hz, 1H), 4.51 (dd, *J*=3, 2 Hz, 1H). ^{13}C NMR (D_2O) δ 60.9, 72.4, 77.6, 175.4, 180.4. MS (FAB) *m/z* 180 (MH^+).

3.1.4. (2*R*,3*S*,4*R*)-3,4-Dihydroxyglutamic acid (7). According to the procedure for the preparation of the compound **6**, deprotection and hydrolysis of the cyanolactam **5a** (670 mg, 1.34 mmol) gave the title compound **7** (140 mg, 58%) as white powder, $[\alpha]_D^{25}=-3.80$ (c 1.08, 18% HCl). ^1H NMR (D_2O) δ 4.05 (d, *J*=5 Hz, 1H), 4.14 (d, *J*=2 Hz, 1H), 4.54 (dd, *J*=5, 2 Hz, 1H). ^{13}C NMR (D_2O) δ 61.9, 71.4, 76.2, 174.5, 180.4. MS (FAB) *m/z* 180 (MH^+).

3.1.5. (3*S*,4*S*)-3,4,5-Triacetoxy-1-(4-methoxybenzyl)-2-pyrrolidinone (8). To a solution of (3*S*,4*S*)-3,4-diacetoxy-1-(4-methoxybenzyl)-2,5-pyrrolidinedione (7.87 g, 16.4 mmol), derived from D-tartaric acid, in methanol (150 mL) was added sodium borohydride (3.14 g, 82.1 mmol) at 0°C. After it was stirred for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and evaporated to dryness to give a hydroxylactam as a white solid. To a solution of the hydroxylactam in pyridine (200 mL) was added acetic anhydride (8.38 g, 82.1 mmol), and the reaction mixture was stirred at room temperature overnight. After evaporation of the solvent, the residue was extracted with chloroform. The organic layer was washed successively with 1 M HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate=50:50) to give the title compounds **8** (8.14 g, 94%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.92 (s, 3H), 2.03 (s, 3H), 2.14 (s, 3H), 3.75 (s, 3H), 4.18 (d, *J*=15 Hz, 1H), 4.61 (d, *J*=15 Hz, 1H), 5.16 (dd, *J*=4, 2 Hz, 1H), 5.30 (d, *J*=4 Hz, 1H), 5.99 (d, *J*=2 Hz, 1H), 6.81 (d, *J*=9 Hz, 2H), 7.14 (d, *J*=9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 19.97 (2 C), 20.05, 43.74, 54.71, 72.75, 75.50, 82.90, 113.62, 126.88, 129.20, 158.88, 167.18, 169.05, 169.12, 169.22. HRMS (EI, 30 eV) *m/z* 379.1288 (M^+, calcd for $C_{18}H_{21}NO_8$ 379.1267).

3.1.6. (3*S*,4*R*)-3,4-Diacetoxy-5-cyano-1-(4-methoxybenzyl)-2-pyrrolidinone (10). To a solution of acetoxylactam **8** (3.78 g, 10.0 mmol) and trimethylsilyl cyanide (1.48 g, 15.0 mmol) in dichloromethane (200 mL) was added a solution of boron trifluoride etherate (2.84 g, 20.0 mmol) in dichloromethane (10 mL) at 0°C under an argon atmosphere, and the reaction mixture was stirred for 5 min. After it was stirred at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous Na_2CO_3 and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate=50:50) to give the title compounds **10** (3.22 g, 93%) as a partially separable mixture of diastereomers. Major isomer: ^1H NMR ($CDCl_3$) δ 2.03 (s, 3H), 2.12 (s, 3H), 3.74 (s, 3H), 3.97 (d, *J*=15 Hz, 1H), 4.00 (d, *J*=5 Hz, 1H), 5.11 (d, *J*=15 Hz, 1H), 5.28 (d, *J*=5 Hz, 1H), 5.42 (dd, *J*=5, 5 Hz, 1H), 6.84 (d, *J*=8 Hz, 2H), 7.17 (d, *J*=8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 20.10, 20.16, 44.83, 50.30, 55.05, 72.75, 72.81, 114.06, 114.34, 125.04, 129.88, 159.61, 166.03, 169.34, 169.56. HRMS (EI, 70 eV) *m/z* 346.1153 (M^+, calcd for $C_{17}H_{18}N_2O_6$ 346.1165). Minor isomer: ^1H NMR ($CDCl_3$) δ 2.07 (s, 6H), 3.68 (s, 3H), 3.98 (d, *J*=15 Hz, 1H), 4.60 (d, *J*=7 Hz, 1H), 4.87 (d, *J*=15 Hz, 1H), 5.22 (dd, *J*=7, 7 Hz, 1H), 5.47 (d, *J*=7 Hz, 1H), 6.79 (d, *J*=8 Hz, 2H), 7.13 (d, *J*=8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 19.93, 19.98, 45.07, 48.43, 54.80, 69.29, 72.06, 112.76, 114.10, 124.65, 129.73, 159.46, 165.52, 169.27, 179.75. HRMS (EI, 70 eV) *m/z* 346.1133 (M^+, calcd for $C_{17}H_{18}N_2O_6$ 346.1165).

3.1.7. (3*S*,4*R*,5*R*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]-5-cyano-1-(4-methoxybenzyl)-2-pyrrolidinone (11) and (3*S*,4*R*,5*S*)-3,4-bis[(*tert*-butyldimethylsilyl)oxy]-5-cyano-1-(4-methoxybenzyl)-2-pyrrolidinone (12). To a solution of cyanolactam **10** (3.22 g, 9.33 mmol) in ethanol (47 mL) was added acetyl chloride (2.19 g, 27.9 mmol), and the solution was stirred at 50°C for 2 h. After evaporation of the solvent, the residue was dissolved in *N*,*N*-dimethylformamide (47 mL). To the solution was added imidazole (2.85 g, 41.9 mmol) and *tert*-butyldimethylchlorosilane (4.21 g, 27.9 mmol), and the solution was stirred at room temperature overnight. The reaction mixture was then diluted with ethyl acetate, washed with water, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel using a mixture of hexane and ethyl acetate (50:50) as an eluent. The fast fraction contained compound **11** (2.43 g, 53%), and further elution gave compound **12** (1.00 g, 22%). The spectral data of compounds **11** and **12** are identical with those of compounds **5a** and **4a**, respectively.

3.1.8. (2*S*,3*R*,4*S*)-3,4-Dihydroxyglutamic acid (13). According to the procedure for the preparation of compound **6**, deprotection and hydrolysis of cyanolactam **11** (183 mg, 3.83 mmol) gave the title compound **13** (280 mg, 40%) as white powder. The spectral data of compound **13** is identical with those of the compounds **7**, $[\alpha]_D^{25}=+4.07$ (*c* 1.08, 18% HCl).

3.1.9. (2*R*,3*R*,4*S*)-3,4-Dihydroxyglutamic acid (14). According to the procedure for the preparation of compound **6**, deprotection and hydrolysis of cyanolactam **12** (2.33 g, 4.95 mmol) gave the title compound **14** (520 mg, 60%) as white powder. The spectral data of compound **14** is identical with those of compounds **6**, $[\alpha]_D^{25}=-8.26$ (*c* 1.08, 18% HCl).

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