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An efficient and stereospecific synthesis of (2*S*,4*S*)-2,4-diaminoglutaric acid

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Abstract

An efficient and stereospecific synthesis of (2*S*,4*S*)-2,4-diaminoglutaric acid **1** starting from *trans*-4-hydroxy-L-proline **2** is presented. The key step involves the combined application of ruthenium tetroxide (RuO_4) oxidation of 4-(*tert*-butoxycarbonylamino)proline derivatives **7** and **8** followed by regioselective ring opening of the resulting lactams **9** and **10** with 1 M LiOH.

Recently, much interest has been focused on the synthesis of unnatural and unusual α-amino acids,[1] since this class of compound has intrinsic biological activity. They can also modify biological activity in a useful way, when incorporated into medicinally important peptides.[2] The development of efficient and stereoselective methods to produce such compounds in enantiomerically pure form from readily available starting materials, is, therefore, crucial. As a part of our research in the asymmetric synthesis of novel α-amino acids,[3] we have been interested in the synthesis of enantiomerically pure 2,4-diaminoglutaric acid **1** as one example of bis(α-amino acids). There are a few reports on the synthesis of **1** and none of them describe stereospecific procedures.[4] More recently, Avenoza et al. reported the highly diastereoselective synthesis of the *meso*- and (2*R*,4*R*)-**1** from Garner's aldehyde employing asymmetric hydrogenation.[4c,d] We describe herein the first stereospecific synthesis of enantiomerically pure (2*S*,4*S*)-2,4-diaminoglutaric acid **1** from readily available *trans*-4-hydroxy-L-proline **2**. Our synthetic approach involved the combined application of ruthenium tetroxide (RuO_4) oxidation[5] of 4-(*tert*-butoxycarbonylamino)proline derivatives **7** and **8** followed by regioselective hydrolysis of the resulting lactams **9** and **10** with 1 M LiOH/THF[6] as outlined in Scheme 1.

Starting from *trans*-4-hydroxy-L-proline **2**, *N*-protection (Boc_2O, Et_3N) followed by esterification with *O*-*tert*-butyl-*N*,*N*′-diisopropylisourea[7] and mesylation (MsCl, pyridine) of the resulting alcohol gave *N*-Boc mesylate **5** in 78% overall yield. Mesylate **5** was subjected to an S_N2 reaction with sodium azide in DMF at 70°C to give **6** in 86% yield. The stereostructure of the stereogenic center at C_4 in **6** was assigned by NOE measurements in the 400 MHz ^{1}H-NMR spectra. Thus, irradiation of C_3-H_α (δ 2.36–2.50) of

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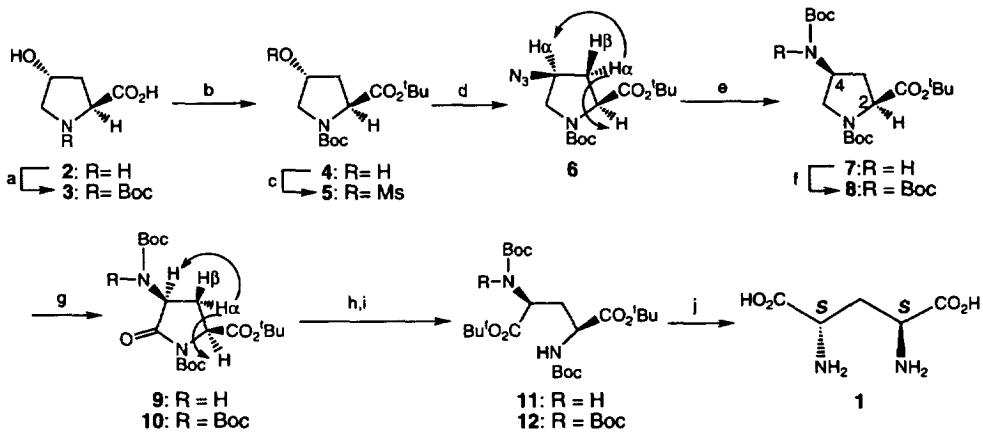

Reagents and Conditions: a) Boc_2O, Et_3N; b) *O-tert*-butyl-*N,N*-diisopropylisourea, THF; c) MsCl, pyridine, 78% (3 steps); d) NaN_3, DMF, 70°C, 86%; e) Pd-C/H_2, Boc_2O, AcOEt, rt, 90%; f) $LiN(TMS)_2$, Boc_2O, CH_3CN, 83%; g) RuO_2ÅE xH_2O, 10% aq. $NaIO_4$, AcOEt, 58% for 9, 88% for 10; h) 1M LiOH/THF, rt; i) *O-tert*-butyl-*N,N*-diisopropylisourea, THF, 56% for 11, 60% for 12 , (each 2 steps) ; j) TFA, CH_2Cl_2, 82%.

Scheme 1.

6 resulted in enhancements of both C_2-H_α (δ 4.21 and 4.31) and C_4-H_α (δ 4.15–4.22) resonances, respectively, which indicated the 2,4-*cis* configuration. Accordingly, the stereostructure of **6** could be rigorously assigned as depicted in Scheme 1. Azide **6** was converted into *N*-Boc amine **7** in 90% yield, employing a one-pot procedure (Boc_2O, Pd–C/H_2, AcOEt)[8] reported by Saito et al. The RuO_4 oxidation of **7** gave the corresponding lactam derivative **9** in 58% yield. The same reaction of *N*-di-Boc derivative **8**, readily prepared from **7** with Boc_2O in the presence of $LiN(TMS)_2$ as base, afforded the corresponding lactam **10** in 88% yield.

The stereochemistry of **9** and **10** was determined by ^{1}H-NMR experiments including difference NOE. Irradiation of C_2-H_α (δ 4.32) of **10** resulted in enhancements of C_3-H_α (δ 2.64) and C_4-H_α (δ 5.01) resonances, respectively, which indicated the 2,4-*cis* configuration. Hydrolytic ring opening of **9** and **10** with 1 M LiOH/THF at room temperature followed by esterification with *O-tert*-butyl-*N,N'*-diisopropylisourea[7] gave *tert*-butyl diester derivatives **11** and **12** in 56 and 60% yields, respectively. The enantiomeric purities of both **11** and **12** were determined to be more than 95% e.e. by 400 MHz ^{1}H-NMR analyses with the chiral NMR shift reagent $Eu(hfc)_3$. Thus, no racemization at the C_2- and C_4-positions in both **11** and **12** under the conditions had taken place. Finally, **11** and **12** were deprotected with TFA to give the desired free amino acid (2*S*,4*S*)-**1** {$[\alpha]_D^{25}$ +45.4 (c 1.0, 1 M HCl), (2*S*,4*S*)-**1**·2HCl: $[\alpha]_D^{25}$ +20.7 (c 1.04, H_2O); lit.[4a] $[\alpha]_D^{25}$ +20.1 (c 1.35, H_2O)} in 56 and 60% yields, respectively, after ion exchange chromatography.

In summary, we have demonstrated an efficient and stereospecific synthesis of enantiomerically pure (2*S*,4*S*)-2,4-diaminogulutaric acid **1** starting from *trans*-4-hydroxy-L-proline **2**. The synthetic strategy outlined in this report would be equally applicable for the synthesis of *ent*- and *meso*-**1** from 4-hydroxy-D-proline or L-allohydroxyproline.

1. Experimental

1.1. General

Melting points were measured on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 automatic digital polarimeter. IR spectra were recorded with a Hitachi 270-30 spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured with a JNM-GSX400 (400 MHz) or a JNM-EX90 (90 MHz) spectrometer. The chemical shifts were expressed in ppm (δ) downfield from tetramethylsilane as an internal standard in $CDCl_3$ solutions, or from 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as an internal standard in D_2O solutions. Coupling constants were expressed in Hz. The following abbreviation are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Electron impact mass spectra (EIMS), high resolution mass spectra (HRMS) and fast atom bombardment mass spectra (FABMS) were obtained with a JMS DX-300 spectrometer. Routine monitoring of reactions was carried out using Merck TLC aluminium sheet silica gel 60 F_{254}. Solvents and commercial reagents were dried and purified before use. Methanol and ethanol were distilled from sodium; tetrahydrofuran was distilled from sodium benzophenone ketyl; dichloromethane and *N,N*-dimethylformamide were distilled from calcium hydride under an N_2 atmosphere. The *trans*-4-hydroxy-L-proline chiral starting material was purchased from the Sigma Chemical Co.

1.2. (2S,4R)-N-tert-*Butoxycarbonyl-4-hydroxyproline* 3

Compound **3** was prepared according to a literature procedure.[9]

1.3. tert-*Butyl* (2S,4R)-N-tert-*butoxycarbonyl-4-hydroxyprolinate* 4

O-tert-Butyl-*N,N'*-diisopropylisourea (22.0 g, 0.11 mol) was added dropwise to a solution of **3**[9] (25.2 g, 0.11 mol) in THF (100 ml) over a period of 10 min at room temperature and then the mixture was heated to 55–60°C for 4 h. An additional isourea (22.0 g, 0.11 mol) was added to the mixture and then the stirring was continued for 16 h. After this period, isourea (6.0 g, 0.03 mol) was added and the mixture was stirred for 30 min. After cooling the mixture, precipitated urea was filtered off and the filtrate was evaporated *in vacuo* to give a residue, which was purified by column chromatography (hexane:ethyl acetate=1:1) to give **4** (29.7 g, 95%) as a colorless oil. $[\alpha]_D^{21}$ −68.9 (c 1.06, MeOH). IR (neat): 3450, 1744, 1698. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.43, 1.45 and 1.46 (18H, each s, $(CH_3)_3\times2$), 1.98–2.08 (1H, m, C_3-H_β), 2.20–2.34 (1H, m, C_3-H_α), 3.40–3.68 (2H, m, C_5-H_2), 4.25–4.30 (1H, m, C_2-H), 4.40–4.46 (1H, m, C_4-H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 27.95, 28.02, 28.36 and 28.42 (each q, $(CH_3)_3\times2$), 38.39 and 39.13 (each t, C_3), 54.59 and 54.67 (each t, C_5), 58.59 and 58.64 (each d, C_2), 69.02 and 69.89 (each d, C_4), 80.25, 81.18 and 81.25 (each s, $C(CH_3)_3\times2$), 154.39 and 154.50 (urethane), 172.20 and 172.30 (C=O). EIMS m/z: 287 (M^+). HRMS: calcd for $C_{14}H_{25}NO_5$ (M^+): 287.1733. Found: 287.35.

1.4. tert-*Butyl* (2S,4R)-N-tert-*butoxycarbonyl-4-oxymethanesulfonylprolinate* 5

Methanesulfonyl chloride (4.8 g, 0.04 mol) was added dropwise to a solution of alcohol **4** (10.0 g, 0.03 mol) in pyridine (60 ml) at 0°C. After stirring for 10 h at 0°C, the solvent was evaporated *in vacuo*. The residue was diluted with 1 M aqueous Na_2CO_3 (40 ml), and the mixture was extracted with ethyl acetate (100 ml). The extract was washed with brine, then dried over Na_2SO_4. Concentration of the solvent *in*

vacuo gave a residue, which was purified by column chromatography (hexane:ethyl acetate=1:1) to give **5** (12.2 g, 96%), as a colorless solid: Recrystallization from isopropyl ether gave an analytical sample of **5** as colorless needles, mp 78–79°C. $[\alpha]_D^{24}$ −49.6 (c 1.40, MeOH). IR (neat): 1754, 1728, 1698. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.41, 1.43, 1.45 and 1.47 (18H, each s, $(CH_3)_3\times2$), 2.18–2.27 (1H, m, C_3-H_β), 2.55–2.68 (1H, m, C_3-H_α), 3.05 (3H, s, SO_2CH_3), 3.68–3.75 (1H, m, C_5-H_β), 3.84–3.90 (1H, m, C_5-H_α), 4.27–4.45 (1H, m, C_2-H), 5.20–5.32 (1H, m, C_4-H). EIMS m/z: 366 (M^++1). Anal. Calcd for $C_{15}H_{27}NO_7S$: C, 49.30; H, 7.45; N, 3.83. Found: C, 49.48; H, 7.53; N, 3.84.

1.5. tert-*Butyl (2S,4S)-4-azido*-N-tert-*butoxycarbonylprolinate* **6**

Sodium azide (11.1 g, 0.17 mol) was added to a solution of mesylate **5** (15.7 g, 0.043 mol) in DMF (60 ml). The mixture was heated at 65–70°C for 8 h. The reaction mixture was diluted with water (40 ml) and the mixture was extracted with ethyl acetate (100 ml). The extract was washed with brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane:ethyl acetate=3:1) to give **6** (11.5 g, 86%) as a colorless oil. $[\alpha]_D^{26}$ −27.5 (c 1.05, MeOH). IR (neat): 2108, 1750, 1710. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.44, 1.47 and 1.49 (18H, each s, $(CH_3)_3\times2$), 2.14–2.20 (1H, m, C_3-H_β), 2.36–2.50 (1H, m, C_3-H_α), 3.43 and 3.48 (1H, each dd, J=11.73, 3.29, C_5-H_β), 3.65 and 3.71 (1H, each dd, J=11.73, 5.86, C_5-H_α), 4.15–4.22 (1H, m, C_4-H), 4.21 and 4.31 (1H, each dd, J=8.79, 3.29, C_2-H). EIMS m/z: 312 (M^+). HRMS: calcd for $C_{14}H_{24}N_4O_4$ (M^+): 312.1797. Found: 312.1778.

1.6. tert-*Butyl (2S,4S)-4*-tert-*butoxycarbonylamino*-N-tert-*butoxycarbonylprolinate* **7**

A mixture of **6** (10.3 g, 0.033 mol), 10% palladium on carbon (0.8 g), and Boc_2O (8.6 g, 0.039 mol) in ethyl acetate (100 ml) was stirred for 3 h at room temperature under an H_2 atmosphere (3 atm). The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give a residue which was purified by column chromatography (hexane:ethyl acetate=3:1) to give a colorless solid. Recrystallization from isopropyl ether gave an analytical sample of **7** as colorless needles, mp 104–105°C. $[\alpha]_D^{24}$ −26.6 (c 1.14, MeOH), IR (neat): 3408, 1742, 1702. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.42, 1.44, 1.46, 1.48 and 1.52 (27H, each s, $(CH_3)_3\times3$), 1.90–2.00 and 2.35–2.50 (2H, m, C_3-H_2), 3.35–3.55 and 3.60–3.68 (2H, m, C_5-H_2), 4.10–4.18 (1H, m, C_2-H), 4.22–4.34 (1H, m, C_4-H), 5.41 and 5.43 (1H, each d, J=7.50, NH). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 27.91, 28.17 and 28.37 (each q, $(CH_3)_3\times3$), 36.44 and 37.51 (each t, C_3), 49.14 and 50.05 (each d, C_2), 52.98 and 53.34 (each t, C_5), 58.69 and 58.72 (each d, C_4), 79.43, 80.25 and 81.89 (each s, $C(CH_3)_3\times3$), 153.78 and 155.10 (urethane), 172.76 (C=O). EIMS m/z: 368 (M^+). Anal. Calcd for $C_{19}H_{34}N_2O_6$: C, 59.03; H, 8.87; N, 7.25. Found: C, 59.94; H, 8.68; N, 7.02.

1.7. tert-*Butyl (2S,4S)-4-(di*-tert-*butoxycarbonyl)amino*-N-tert-*butoxycarbonylprolinate* **8**

Lithium bis(trimethylsilyl)amide ($LiN(TMS)_2$) (18 ml, 0.018 mol) was added to a solution of **7** (6.0 g, 0.016 mol) in dry CH_3CN (40 ml) at −15°C. The mixture was stirred for 30 min, then Boc_2O (3.9 g, 0.018 mol) was added. After stirring for 2 h, the mixture was quenched with brine and then concentrated *in vacuo*. Water (20 ml) was added and the mixture was extracted with ethyl acetate (80 ml). The extract was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue which was purified by column chromatography (hexane:ethyl acetate=2:1) to give **8** (6.3 g, 83%) as a colorless oil. $[\alpha]_D^{25}$ −26.6 (c 1.42, MeOH). IR (neat): 1814, 1748, 1712. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.43, 1.46, 1.48, 1.50 and 1.53 (36H, each s, $(CH_3)_3\times4$), 2.28–2.55 (2H, m, C_3-H_2), 3.64 and 3.72

(each 1H, each t, J=9.90, C_5-H_2), 4.12 and 4.19 (1H, each t, J=8.43, C_2-H), 4.59–4.70 (1H, m, C_4-H). EIMS m/z: 486 (M^+). HRMS: calcd for $C_{24}H_{42}N_2O_8$ (M^+): 486.2940. Found: 486.2916.

1.8. tert-*Butyl (2S,4S)-4-*tert-*butoxycarbonylamino-*N-tert-*butoxycarbonylpyroglutamate* ***9***

A solution of **7** (4.1 g, 0.01 mol) in ethyl acetate (60 ml) was added to a mixture of $RuO_2 \cdot xH_2O$ (0.2 g) and 10% aqueous $NaIO_4$ (60 ml). The solution was stirred vigorously for 6 h at room temperature. The layer was separated and the aqueous layer was extracted with ethyl acetate (80 ml). The extract was treated with 2-propanol (0.2 ml). Black-colored RuO_2 which precipitated from the solution was filtered off and the filtrate was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue which was purified by column chromatography (hexane:ethyl acetate=2:1) to give **9** (2.5 g, 58%) as a colorless solid. Recrystallization from ethyl acetate:isopropyl ether gave an analytical sample of **9** as colorless prisms, mp 180–181°C. $[\alpha]_D^{24}$ −44.7 (c 1.02, MeOH). IR (KBr): 3440, 1780, 1742, 1724, 1698. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.44, 1.48 and 1.52 (27H, each s, $(CH_3)_3\times3$), 1.72–1.82 (1H, m, C_3-H_β), 2.83–2.94 (1H, m, C_3-H_α), 4.28–4.40 (2H, m, C_2- and C_4-H), 5.24 (1H, br s, NH). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 27.69, 27.72, 27.88 and 27.91 (each q, $(CH_3)_3\times3$), 30.50 (t, C_3), 52.38 (d, C_2), 56.82 (d, C_4), 80.38, 82.61 and 84.13 (each s, $C(CH_3)_3\times3$), 149.08 and 155.53 (urethane), 169.74 and 170.94 (C=O). EIMS m/z: 400 (M^+). Anal. Calcd for $C_{19}H_{32}N_2O_7$: C, 56.98; H, 8.05; N, 7.00. Found: C, 56.96; H, 8.19; N, 6.94.

1.9. tert-*Butyl (2S,4S)-4-(di-*tert-*butoxycarbonyl)amino-*N-tert-*butoxycarbonylpyroglutamate* ***10***

Treatment of **8** (5.4 g, 0.011 mol) under the same conditions as described above gave **10** (4.8 g, 88%) as a colorless oil. $[\alpha]_D^{25}$ −15.7 (c 1.08, MeOH). IR (neat): 1810, 1775 1745, 1720, 1700. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.49, 1.51 and 1.53 (36H, each s, $(CH_3)_3\times4$), 2.09 (1H, ddd, J=13.56, 9.16, 8.43, C_3-H_β), 2.64 (1H, ddd, J=13.56, 10.53, 9.90, C_3-H_α), 4.32 (1H, dd, J=9.89, 8.43, C_2-H), 5.01 (1H, dd, J=10.53, 9.16, C_4-H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 26.83 (t, C_3), 27.76, 27.92 and 27.98 (each q, $(CH_3)_3\times4$), 55.68 (d, C_2), 56.24 (d, C_4), 82.17, 83.54 and 84.00 (each s, $C(CH_3)_3\times4$), 149.41 and 151.25 (urethane), 168.98 and 169.07 (C=O). EIMS m/z: 500 (M^+). HRMS: calcd for $C_{24}H_{40}N_2O_9$ (M^+): 500.2734. Found: 500.2702.

1.10. tert-*Butyl (2S,4S)-2,4-di-*tert-*butoxycarbonylaminoglutarate* ***11***

To a solution of **9** (3.9 g, 9.7 mmol) in THF (30 ml) was added dropwise 1 M solution (30 ml) of lithium hydroxide at 0°C. After stirring for 2 h, the organic layer was evaporated *in vacuo*. The aqueous layer was carefully acidified with 10% aqueous citric acid to pH 4 at 0°C. The aqueous layer was extracted with ethyl acetate (60 ml) and the extract was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a crude carboxylic acid (3.7 g) as a colorless oil, which was directly used for the next esterification without purification. The crude carboxylic acid (3.7 g) was dissolved in dry THF (40 ml), and *O-tert*-butyl-*N,N'*-diisopropylisourea (1.8 g, 8.6 mmol) dropwise over a period of 10 min at room temperature and then the mixture was heated to 55–60°C for 4 h. Additional isourea (1.8 g, 8.6 mmol) was added and then the stirring was continued for 16 h. After this period, isourea (0.53 g, 2.6 mmol) was added and the mixture was stirred for 30 min. After cooling the mixture, precipitated urea was filtered off and the filtrate was evaporated *in vacuo* to give a residue which was purified by column chromatography (hexane:ethyl acetate=3:1) to give **11** as a colorless solid. Recrystallization from isopropyl ether gave an analytical sample of **11** as colorless prisms, mp 86–87°C. $[\alpha]_D^{25}$ −25.5 (c 1.50,

MeOH). IR (KBr): 3400, 1748, 1732, 1720, 1702. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.45 and 1.47 (36H, each s, $(CH_3)_3\times4$), 1.90–2.18 (2H, m, C_3-H_2), 4.08–4.26 (2H, m, C_2- and C_4-H), 5.26 (2H, br s, NH×2). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 27.99 and 28.33 (each q, $(CH_3)_3\times4$), 34.85 (t, C_3), 51.70 (d, C_2 and C_4), 79.84, 82.14 (each s, $C(CH_3)_3\times4$), 155.45 (s, urethane), 171.23 (s, C=O). EIMS m/z: 475 (M^++1). Anal. Calcd for $C_{23}H_{42}N_2O_8$: C, 58.21; H, 8.92; N, 5.90. Found: C, 56.02; H, 8.78; N, 5.77.

1.11. tert-*Butyl (2S,4S)-4-di*-tert-*butoxycarbonylamino-2*-tert-*butoxycarbonylaminoglutarate* ***12***

The same treatment of **10** (4.3 g, 8.6 mmol) as described for the preparation of **11** from **9** gave **12** (2.9 g, 60%) as a colorless viscous oil. $[\alpha]_D^{24}$ −18.8 (c 1.02, MeOH). IR (KBr): 3410, 1788, 1734, 1704. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.44, 1.46, 1.48 and 1.51 (45H, each s, $(CH_3)_3\times5$), 2.10–2.20 and 2.65–2.77 (each 1H, m, C_3-H_2), 4.32–4.43 (1H, m, C_2-H), 4.89 (1H, dd, J=7.70, 5.50, C_4-H), 5.23 (1H, br d, J=8.06, NH). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 27.98, 28.05, 28.10 and 28.39 (each q, $(CH_3)_3\times5$), 32.84 (t, C_3), 52.27 and 52.30 (each d, C_2), 55.94 and 56.04 (each d, C_4), 79.60, 81.67, 81.90, 82.00 and 83.10 (each s, $C(CH_3)_3\times5$), 152.24 and 155.53 (urethane), 169.32 and 171.38 (C=O). HRMS: calcd for $C_{28}H_{50}N_2O_{10}$ (M^+): 574.3466. Found: 574.3428.

1.12. (2S,4S)-2,4-Diaminoglutaric acid ***1***

(a) From **11**: trifluoroacetic acid (5 ml) was added to a stirred solution of **11** (1.6 g, 3.4 mmol) in CH_2Cl_2 (30 ml) at 0°C. The reaction mixture was stirred for 1 h and then the solvent was evaporated *in vacuo*. The residue was dissolved in water (2 ml) and purified by Dowex 50 wx8 (50–100 mesh) ion exchange column chromatography (water, then 5% aqueous ammonia) to give (2*S*,4*S*)-**1** (0.45 g, 82%) as a white solid. Recrystallization from 60% aqueous ethanol gave an analytical sample of **1** as colorless prisms, mp>300°C; $[\alpha]_D^{25}$ +45.4 (c 1.00, 1 M HCl). IR (KBr): 3650–2450, 1688, 1610, 1584, 1554. ^{1}H-NMR (400 MHz, D_2O): δ 2.34 (2H, t, J=6.60, C_3-H_2), 3.95 (2H, t, J=6.60, C_2- and C_4-H). ^{13}C-NMR (90 MHz, D_2O): δ 34.56 (t, C_3), 56.15 (d, C_2 and C_4), 176.33 (C=O). Anal. Calcd for $C_5H_{10}N_2O_4$: C, 37.03; H, 6.22; N, 17.28. Found: C, 36.82; H, 6.20; N, 17.02. (2*S*,4*S*)-**1**. 2HCl: mp 190–192°C (decomp.); $[\alpha]_D^{23}$ +20.7 (c 1.04, H_2O), lit.[4a] $[\alpha]_D^{25}$ +20.1 (c 1.35, H_2O).

(b) From **12**: treatment of **12** (1.6 g, 3.4 mmol) under the same conditions as described above gave (2*S*,4*S*)-**1** (0.45 g, 82%).

References

1. (a) Williams, R. M. "Synthesis of Optically Active α-Amino Acids", Vol. 7 of *Organic Chemistry Series*, Ed. Baldwin, J. E. and Magnus, P. D., Pergamon Press, Oxford, 1989. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650.
2. Gante, G. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699–1730 and references cited therein.
3. Tanaka, K.; Sawanishi, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1641–1656. Tanaka, K.; Iwabuchi, H.; Sawanishi, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2271–2279. Tanaka, K.; Suzuki, H.; Sawanishi, H. *Heterocycles*, **1996**, *43*, 205–219.
4. (a) Belokon, Yu. N.; Chernoglazova, N. I.; Batsanov, A. S.; Garbalinskaya, N. S.; Bakhmutov, V. I.; Struchkov, Yu. T.; Belikov, V. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1987**, *4*, 852–857. (b) Mulzer, J.; Schroder, F.; Lobbia, A.; Buschmann, J.; Luger, P. *Angew. Chem. Int. Ed. Eng.* **1994**, *33*, 1737–1739. (c) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1996**, *7*, 1555–1558. (d) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1997**, *8*, 863–871.
5. Yoshifuji, S.; Tanaka, K.; Kawai, T.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3873–3878.
6. Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424–2426. Durand, X.; Hudhomme, P.; Khan, J. A.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1131–1139 and references cited therein.
7. Mathias, L. J. *Synthesis* **1979**, 561–576.

8. Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837–838.
9. Bowers-Nemia, M. M.; Joullie, M. M. *Heterocycles* **1983**, *20*, 817–828.