Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 3837–3843

TETRAHEDRON: *ASYMMETRY*

Stereospecific synthesis of differentially protected (2*S*,4*S*)-2,4-diaminoglutaric acid suitable for incorporation into peptides

Ken-ichi Tanaka* and Hiroyuki Sawanishi

Faculty of Pharmaceutical Science, Hokuriku University, Ho-3, Kanagawa-machi, Kanazawa 920-1181, Japan

Received 22 August 2000; accepted 21 September 2000

Abstract

The first synthesis of differentially protected (2*S*,4*S*)-2,4-diaminoglutaric acids **2** and **3** suitable for incorporation into peptides has been accomplished in a completely stereospecific manner in seven steps (overall yield 25–28%) from *tert*-butyl (2*S*,4*S*)-4-azido-*N*-*tert*-butoxycarbonylprolinate **5**.

1. Introduction

Recently, much interest has been focused on the synthesis of unnatural and unusual α-amino acids,[1] since this class of compound has an intrinsic biological activity. They can also modify biological potency and improve metabolic stability in a useful way when incorporated into medicinally important peptides.[2] In particular, the incorporation of α-amino acids with a functional group that can act as a receptor ligand has much current attention.[3] Therefore, the development of efficient and stereoselective synthetic methods to produce such types of α-amino acids in enantiomerically pure form from readily available starting materials is crucial.

We have previously reported a stereospecific synthesis of free (2*S*,4*S*)-2,4-diaminoglutaric acid [(2*S*,4*S*)-DAG **1**] (Fig. 1) as one example of bis(α-amino acids) using ruthenium tetroxide (RuO_4) oxidation[4] of *tert*-butyl (2*S*,4*S*)-4-(di-Boc-amino)-*N*-Boc-prolinate (Boc = *tert*-butoxycarbonyl), followed by regioselective hydrolysis and further simultaneous deprotection.[4a] While several syntheses of homochiral **1** have been reported,[5] to date there has been no report of stereospecific synthesis of their protected derivatives suitable for incorporation into peptide. Among them, Mulzer et al. have reported a diastereoselective synthesis of protected (2*S*,4*S*)-DAG from L-glutamic acid, which was employed as a building block for peptidomimetics.[5b] The

* Corresponding author. E-mail: k-tanaka@hokuriku-u.ac.jp

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00386-4

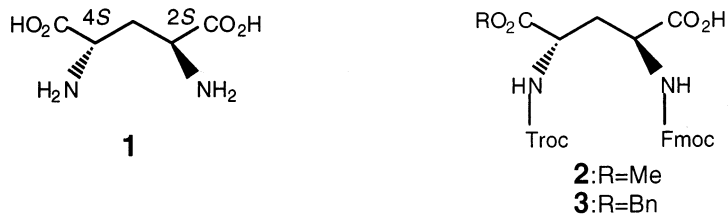


Figure 1.

synthesis of DAG-containing peptides or peptidomimetics requires a supply of differentially protected DAG in which the N- and C-termini can be selectively deprotected.

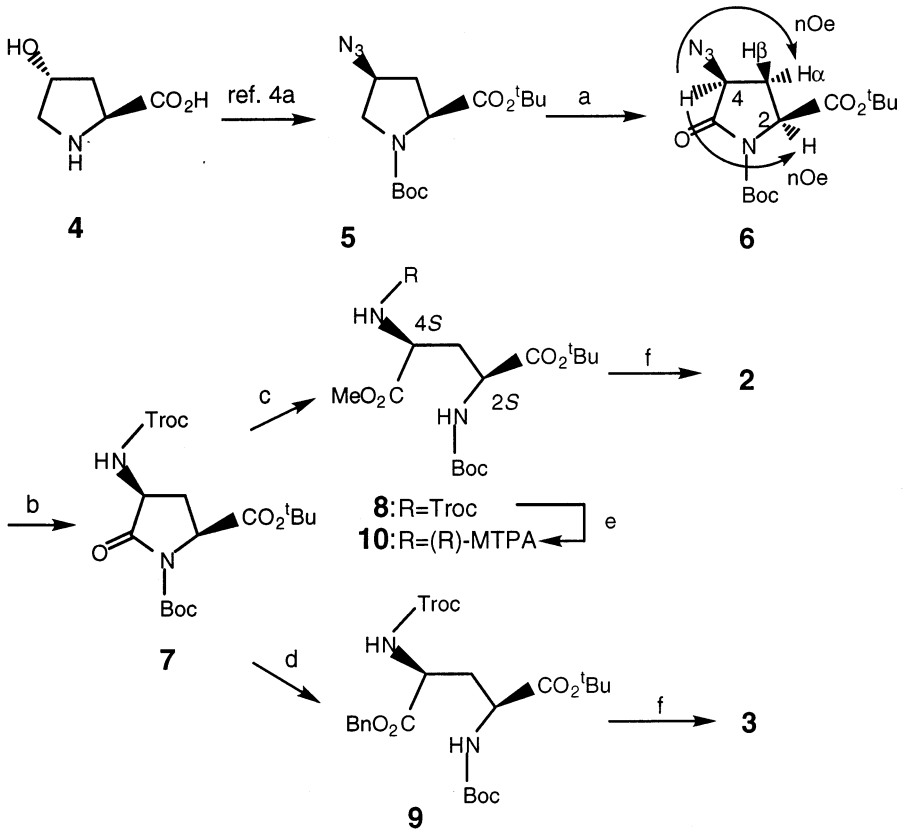
As part of our research in the asymmetric synthesis of novel α-amino acids,[6] we herein report the further exploitation of our method for the synthesis of differentially protected (2*S*,4*S*)-DAG derivatives **2** and **3** suitable for incorporation during the assembly of the peptide backbone (Fig. 1).

2. Results and discussion

We planned to synthesize *tert*-butyl *N*-Boc-4-azidopyroglutamate **6** as the key intermediate, in which the functionality at the C_4-position can be easily converted into any kind of protected side chain α-amino acid moiety of target (2*S*,4*S*)-DAG derivatives **2** and **3**, and also the *N*-Boc protecting group can be replaced with the 9-fluorenylmethoxycarbonyl (Fmoc) group during subsequent steps.

Our synthetic route for target α-amino acids **2** and **3** is shown in Scheme 1. The synthesis of the key intermediate **6** started with *tert*-butyl (2*S*,4*S*)-4-azido-*N*-Boc-prolinate **5**, which was prepared from *trans*-4-hydroxy-L-proline **4** in a four-step sequence with 67% overall yield according to our previously reported procedure.[4a] The RuO_4 oxidation of **5** gave the corresponding lactam derivative **6** in 75% yield. The stereochemical assignment of **6** was determined by ^{1}H NMR experiments including difference NOE, as illustrated for **6** (Scheme 1). Thus, irradiation of the C_4-H (δ 4.42) resulted in enhancements of both the signals due to the C_3-Hα (δ 2.61) and C_2-H (δ 4.20) and irradiation of the C_3-H_β (δ 1.84) gave no enhancement of the signal due to the C_2-H. Accordingly, the C_2-H and C_4-H in **6** was assigned to have *cis*-configuration. The absolute configuration of **6** was unambiguously determined as (2*S*,4*S*)-**6**. Hydrogenation of **6** with 10% Pd–C, followed by *N*-protection with 2,2,2-trichloroethoxycarbonyl chloride (Troc-Cl) gave *tert*-butyl *N*-Boc-4-(Troc-amino)pyroglutamate **7** in 72% yield over two steps. Next, hydrolytic ring opening of **7** with 1 M LiOH/THF at room temperature, followed by esterification with CH_2N_2 gave (2*S*,4*S*)-2,4-diamino-4-methyl ester **8** in 78% yield over two steps.

The enantiomeric purity of **8** was determined to be more than 95% ee by 400 MHz ^{1}H NMR analysis of its Mosher's amide derivative **10**. Thus, removal of the Troc protection in **8** with zinc dust in acetic acid,[7] followed by acylation with (*R*)-MTPA chloride[8] in the presence of 4-dimethylaminopyridine gave **10** as a single diastereoisomer in 86% yield over two steps. No epimerization of both the stereogenic centers at the C_2- and C_4-positions in **8** had occurred under the conditions. Similar hydrolysis of **7**, followed by esterification with benzyl bromide (BnBr) in the presence of K_2CO_3 and a catalytic amount of NaI in DMF afforded (2*S*,4*S*)-2,4-diamino-4-benzyl ester **9** in 72% yield over two steps.



Scheme 1. Reagents and conditions: (a) $RuO_2 \cdot xH_2O$, 10% aq. $NaIO_4$/AcOEt, 75%; (b) (i) 10% Pd–C/H_2, MeOH; (ii) Troc-Cl, Et_3N, CH_2Cl_2, 0°C (72%, two steps); (c) (i) 1 M LiOH/THF, rt, (ii) CH_2N_2, MeOH (78%, two steps); (d) (i) 1 M LiOH/THF, rt, (ii) BnBr, NaI, K_2CO_3, DMF, rt (72%, two steps); (e) (i) zinc dust, AcOH, rt, (ii) (*R*)-MTPA-Cl, 4-DMAP, THF (86%, two steps); (f) (i) TFA, CH_2Cl_2, rt, (ii) Fmoc-Cl, Na_2CO_3, H_2O/THF, 0°C (68% for **2**, 65% for **3**, each two steps)

The final step in our synthesis involved removal of the *N*-Boc and the *tert*-butyl ester protecting groups in **8** and **9**, and subsequent reprotection of the C_2-amino function with an Fmoc group. Thus, both **8** and **9** were treated with trifluoroacetic acid (TFA) at room temperature and, immediately after, reprotected with Fmoc-Cl in the presence of Na_2CO_3 in THF/H_2O to afford the enantiomerically pure target Fmoc bis(α-amino acid) **2**, $[\alpha]_D^{22}$ −24.5 (*c* 1.80, MeOH), in 68% yield from **8**, and **3**, $[\alpha]_D^{25}$ −25.0 (*c* 1.20, MeOH), in 65% from **9**, respectively, after silica gel column chromatography.

3. Conclusion

From the readily available *tert*-butyl (2*S*,4*S*)-4-azido-*N*-Boc-prolinate **5** we have accomplished the first synthesis of differentially protected chiral (2*S*,4*S*)-DAGs **2** and **3** in a completely stereospecific manner.

4. Experimental

4.1. 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. Infrared (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 internal standard in $CDCl_3$ solutions. Coupling constants were expressed in Hz. The following abbreviations 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 JMS DX-300 spectrometer. Routine monitoring of reactions was carried out using Merck TLC aluminium sheet silica gel 60 F_{254}. Solvents were dried and purified before use. Methanol was distilled from sodium; tetrahydrofuran was distilled from sodium benzophenone ketyl; dichloromethane and *N*,*N*-dimethylformamide were distilled from calcium hydride under a N_2 atmosphere. The *trans*-4-hydroxy-L-proline used as homochiral starting material was purchased from Sigma Chemical Co.

tert-Butyl (2*S*,4*R*)-4-azido-*N*-*tert*-butoxycarbonylprolinate **5** was prepared according to a literature procedure.[4a]

4.2. tert-*Butyl (2*S,*4*S*)-4-azido*-N-tert-*butoxycarbonylpyroglutamate* **6**

A solution of **5** (8.0 g, 25 mmol) in ethyl acetate (80 ml) was added to a mixture of $RuO_2{\cdot}xH_2O$ (0.2 g) and 10% aqueous $NaIO_4$ (120 ml). The solution was stirred vigorously for 15 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 = 4:1) to give **6** (6.0 g, 72%) as a colorless solid. Recrystallization from isopropyl ether gave an analytical sample of **6** as colorless needles, mp 105–106°C. $[\alpha]_D^{26}$ −208.2 (*c* 1.53, MeOH). IR (KBr): 2109, 1781, 1735, 1702. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49, 1.53 (each 9H, s, $OC(CH_3)_3\times2$), 1.84 (1H, ddd, $J_{3\beta,3\alpha}=13.92$, $J_{3\beta,2}=5.86$, $J_{3\beta,4}=5.50$, C_3-H_β), 2.61 (1H, dd, $J=13.92$, 8.80, C_3-H_α), 4.20 (1H, dd, $J=8.80$, 5.86, C_2-H), 4.42 (1H, dd, $J=8.80$, 5.50, C_4-H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 27.86, 28.21 (each q, $OC(\underline{C}H_3)_3\times2$), 57.24 (d, C_2), 59.02 (d, C_4), 82.78, 84.24 (each s, $O\underline{C}(CH_3)_3$), 149.02 (urethane C=O), 169.04 (s, lactam C=O), 169.19 (s, ester C=O). EIMS *m*/*z*: 327 ($M+1^+$). Anal. calcd for $C_{14}H_{22}N_4O_5$: C, 51.52; H, 6.80; N, 17.17. Found: C, 51.48; H, 6.76; N, 17.30.

4.3. tert-*Butyl (2*S,*4*S*)-4-(2,2,2-trichloroethoxycarbonylamino)*-N-tert-*butoxycarbonylpyroglutamate* **7**

A mixture of **6** (3.0 g, 19.9 mmol) and 10% palladium on carbon (0.5 g) in methanol (80 ml) was stirred for 4 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 directly used

for the next acylation without purification. Triethylamine (3.0 g, 29.8 mmol) and 2,2,2-trichloroethoxycarbonyl chloride (5.05 g, 23.9 mmol) were added to the solution of the resulting residue in dichloromethane (80 ml) and the mixture was stirred at 0°C for 6 h. The mixture was washed successively with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (benzene/ethyl acetate = 5:1) to give **7** (6.8 g, 72%) as a colorless solid. Recrystallization from isopropyl ether gave an analytical sample of **7** as colorless needles, mp 108–108°C. $[\alpha]_D^{22}$ −39.8 (*c* 1.32, MeOH). IR (KBr): 3380, 1808, 1742, 1732. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42, 1.52 (each 9H, each s, $OC(CH_3)_3\times2$), 1.80–1.92 (1H, m, C_3-H_β), 2.85–2.96 (1H, m, C_3-H_α), 4.37–4.48 (2H, m, C_2- and C_4-H), 4.68 and 4.77 (2H, each d, J = 11.73, CH_2CCl_3), 5.87 (1H, d, J = 6.23, NH). ^{13}C NMR (90 MHz, $CDCl_3$): δ 27.86, 27.90 (each q, $OC(\underline{C}H_3)_3\times2$), 29.73 (t, C_3), 52.73 (d, C_2), 56.76 (d, C_4), 74.83 (t, $\underline{C}H_2CCl_3$), 82.86, 84.30 (each s, $O\underline{C}(CH_3)_3\times2$), 148.97, 154.45 (each s, urethane C=O), 169.73, 170.06 (each s, C=O). EIMS *m*/*z*: 476 ($M+1^+$). Anal. calcd for $C_{17}H_{25}N_2O_7Cl_3$: C, 42.91; H, 5.29; N, 5.88. Found: C, 42.78; H, 5.06; N, 5.72.

*4.4. (2*S,*4*S*)-2-(*tert-*Butoxycarbonylamino)-4-methoxycarbonyl-4-(2,2,2-trichloroethoxycarbonylamino)pentanedioic acid 1-*tert-*butyl ester* ***8***

To a solution of **7** (5.8 g, 12 mmol) in THF (50 ml) was added dropwise a 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 (80 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 (5.2 g) as a colorless oil, which was directly used for the next esterification without purification. The crude carboxylic acid (5.2 g) was treated with excess CH_2N_2 in MeOH for 3 h at 0°C. Concentration of the solvent in vacuo gave a residue which was purified by column chromatography (benzene/ethyl acetate = 4:1) to give **8** (5.0 g, 78%) as a colorless oil. $[\alpha]_D^{22}$ −24.5 (*c* 1.80, MeOH). IR (neat): 3420, 1730, 1682. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45, 1.47 (18H, each s, $OC(CH_3)_3\times2$), 2.12–2.23 (2H, m, C_3-H_2), 3.77 (3H, s, CO_2CH_3), 4.20–4.43 (2H, m, C_2- and C_4-H), 4.69, 4.79 (each 1H, each d, J = 12.09, CH_2CCl_3), 5.95 (2H, each s, NH×2). ^{13}C NMR (90 MHz, $CDCl_3$): δ 27.95, 28.32 (each q, $OC(\underline{C}H_3)_3\times2$), 34.93 (t, C_3), 51.24 (d, C_2), 51.71 (d, C_4), 52.72 (q, CO_2CH_3), 74.68 (t, $\underline{C}H_2CCl_3$), 80.29, 82.74 (each s, $\underline{C}(CH_3)_3$), 154.23, 155.68 (each s, urethane C=O), 170.87, 171.66 (each s, ester C=O). HRMS: calcd for $C_{18}H_{29}N_2O_8Cl_3$ (M^+): 506.0989. Found: 506.1016.

*4.5. (2*S,*4*S*)-4-Benzyloxycarbonyl-2-(*tert-*butoxycarbonylamino)-4-(2,2,2-trichloroethoxycarbonylamino)pentanedioic acid 1-*tert-*butyl ester* ***9***

To a solution of **7** (4.06 g, 8.8 mmol) in THF (50 ml) was added dropwise a 1 M solution (25 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 (80 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 (4.02 g) as a colorless oil and then DMF (50 ml), K_2CO_3 (1.4 g, 10 mmol), NaI (0.2 g, 1.3 mmol) and benzyl bromide (4.4 g, 25 mmol) were successively added to the resulting residue. The

reaction mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with H_2O and extracted with ethyl acetate (80 ml). The extract was washed with brine, 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 **9** (3.70 g, 72%) as a colorless oil. $[\alpha]_D^{25}$ −25.0 (*c* 1.20, MeOH). IR (neat): 3430, 1740. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43, 1.45 (each 9H, each s, $OC(CH_3)_3\times2$), 2.10–2.21, 2.27–2.38 (2H, m, C_3-H_2), 4.20–4.30, 4.36–4.48 (2H, m, C_2- and C_4-H), 4.66, 4.77 (each 1H, each d, J = 12.09, CH_2CCl_3), 5.15, 5.26 (each 1H, each d, J = 12.46, CH_2Ph), 5.22, 5.92 (each 1H, br s, NH×2), 7.28–7.40 (5H, m, aromatic-H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 27.94, 28.30 (each q, $OC(\underline{C}H_3)_3\times2$), 34.72 (t, C_3), 51.23 (d, C_2), 51.84 (d, C_4), 67.59 (t, CH_2Ph), 74.67 (t, $\underline{C}H_2CCl_3$), 80.26, 82.71 (each s, $\underline{C}(CH_3)_3$), 128.34, 128.40, 128.62, 135.09 (aromatic-C), 154.20, 155.61 (each s, urethane C = O), 170.84, 171.04 (each s, ester C = O). HRMS: calcd for $C_{24}H_{33}N_2O_8Cl_3$ (M^+): 582.1302. Found: 582.1280.

*4.6. (2*S*,4*S*)-4-[(*R*)-2-Methoxy-2-(trifluoromethyl)phenylacetylamino]-4-methoxycarbonyl-2-(*tert*-butoxycarbonyl)pentanedioic acid 1-*tert*-butyl ester **10***

Zinc dust (0.3 g) was added to a solution of **8** (0.50 g, 0.1 mmol) in glacial acetic acid (5 ml) and the mixture was stirred at room temperature for 1.5 h. Zinc was filtered off and the filtrate was carefully basified with 10% aqueous Na_2CO_3 at 0°C. The aqueous layer was extracted with ethyl acetate (50 ml) and the extract was washed with brine, and dried over Na_2SO_4. Concentration of the solvent in vacuo gave a crude amine (0.30 g) as a pale brown oil, which was directly used for the next acylation without purification. The crude amine (0.30 g) was dissolved in CH_2Cl_2 (15 ml). 4-Dimethylaminopyridine (0.16 g, 1.3 mmol) and (*R*)-2-methoxy-2-(trifluoromethyl)phenylacetyl chloride [(*R*)-MTPA-Cl] (0.35 g, 0.1 mmol) were added to the solution at 0°C and then the mixture was stirred for 4 h. The reaction mixture was diluted with 10% aqueous Na_2CO_3 and extracted with ethyl acetate (50 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 (benzene/ethyl acetate = 9:1) to give **10** (0.46 g, 86%) as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43, 14.7 (each 9H, each s, $OC(CH_3)_3\times2$), 2.16–2.38 (2H, m, C_3-H_2), 3.44 (3H, s, OCH_3), 3.74 (3H, s, CO_2CH_3), 4.05–4.12 (1H, m, C_2-H), 4.48–4.58 (1H, m, C_4-H), 5.23 (1H, br d, J = 6.23, NHBoc), 7.32–7.60 (5H, m, aromatic-H), 7.64 (1H, br d, J = 6.23, NH-MTPA). ^{13}C NMR (90 MHz, $CDCl_3$): δ 27.95, 28.26 (each q, $OC(\underline{C}H_3)_3$), 34.30 (t, C_3), 50.12 (d, C_2), 51.48 (d, C_4), 52.62 (q, $CO_2\underline{C}H3$), 55.04 (q, OCH_3), 80.14, 80.20 (each s, $O\underline{C}(CH_3)_3\times2$), 127.96, 128.54, 129.56 (aromatic-C), 155.54 (s, urethane C = O), 166.65 (NHCO), 170.69, 171.36 (each s, ester C = O).

*4.7. (2*S*,4*S*)-2-(9-Fluorenylmethoxycarbonylamino)-4-(2,2,2-trichloroethoxycarbonylamino)-pentanedioic acid 5-methyl ester **2***

Trifluoroacetic acid (8 ml) was added to a stirred solution of **8** (2.2 g, 4.4 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred at room temperature for 3 h. The solvent was evaporated in vacuo and ether (10 ml) was added and subsequently evaporated three times until the residue became a white solid. The solid was dissolved in THF (15 ml), 10% aqueous Na_2CO_3 (15 ml) was added, followed by 9-fluorenylmethoxycarbonyl chloride (1.22 g, 4.7 mmol). After stirring at room temperature for 12 h, the mixture was acidified with 10% HCl and diluted with ethyl acetate (40 ml). The organic layer 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 (chloroform/methanol/acetic acid = 5:1:1) to give **11** (1.7 g, 68%) as a colorless solid, mp 96–97°C. $[\alpha]_D^{21}$ −24.0 (*c* 1.00, MeOH). IR (KBr): 3540, 1730. ^{1}H NMR (400 MHz, CD_3OD): δ 2.25–2.36 (2H, m, C_3-H_2), 3.73 (3H, s, CO_2CH_3), 4.17–4.46 (5H, m, C_2-H, C_4-H, and FmocC$\underline{H}$C$\underline{H}_2$), 4.73, 4.77 (2H, each d, J = 11.73, CH_2CCl_3), 7.28–7.80 (8H, m, Fmoc aromatic-H). ^{13}C NMR (90 MHz, CD_3OD): δ 33.64 (t, C_3), 51.86 (d, C_2), 52.37 (d, C_4), 52.91 (q, CO_2CH_3), 54.30 (d, Fmoc$\underline{C}$HCH$_2$), 68.07 (t, FmocCH$\underline{C}$H$_2$), 120.69, 126.09, 126.21, 127.99, 128.54, 128.63, 142.26, 142.29, 144.92, 145.08 (aromatic-C), 156.51, 158.46 (each s, urethane C=O), 173.47, 174.99 (each s, C=O). FABMS *m*/*z*: 574 (M+1$^+$). Anal. calcd for $C_{24}H_{23}N_2O_8Cl_3$: C, 50.23; H, 4.04; N, 4.88. Found: C, 50.08; H, 4.01; N, 4.63.

4.8. (2S,4S)-2-(9-Fluorenylmethoxycarbonylamino)-4-(2,2,2-trichloroethoxycarbonylamino)-pentanedioic acid 5-benzyl ester ***3***

The same treatment of **9** (1.6 g, 2.7 mmol) as described for the preparation of **2** from **8** gave **3** (1.2 g, 65%) as a colorless solid, mp 84–85°C. $[\alpha]_D^{25}$ −16.6 (*c* 1.10, MeOH). IR (KBr): 3546, 1724. ^{1}H NMR (400 MHz, CD_3OD): δ 2.25–2.46 (2H, m, C_3-H), 4.10–4.46 (5H, m, C_2-H, C_4-H, FmocC$\underline{H}$C$\underline{H}_2$), 4.68, 4.74 (2H, each d, J = 11.73, CH_2CCl_3), 5.08, 5.16 (2H, each d, J = 12.46, CH_2Ph), 5.73, 6.12 (2H, each d, J = 6.23, NH×2), 7.22–7.78 (13H, aromatic-H). ^{13}C NMR (90 MHz, CD_3OD): δ 34.09 (t, C_3), 47.06 (d, Fmoc$\underline{C}$H), 50.59 (d, C_2), 51.55 (d, C_4), 67.39 (t, Fmoc CH$\underline{C}$H$_2$), 67.78 (t, CH_2Ph), 95.23 (s, CCl_3), 120.00, 124.93, 125.08, 127.12, 127.77, 128.34, 128.60, 128.66, 134.85, 141.28, 143.62 (aromatic-C), 154.46, 156.42 (each s, urethane C=O), 171.07, 174.66 (each s, C=O). FABMS *m*/*z*: 650 (M+1$^+$). Anal. calcd for $C_{30}H_{27}N_2O_8Cl_3$: C, 55.44; H, 4.18; N, 4.31. Found: C, 55.23; H, 4.01; N, 4.42.

References

1. (a) Williams, R. M. In *Synthesis of Optically Active α-Amino Acids*, *Vol. 7 of Organic Chemistry Series*; Baldwin, J. E.; Magnus, P. D., Eds.; Pergamon Press: Oxford, 1989. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650. (c) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599. (d) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
2. Gante, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699–1730 and references cited therein.
3. (a) Jurgens, A. R. *Tetrahedron Lett.* **1992**, *33*, 4727–4730. (b) Yokum, T. S.; Bursavich, M. G.; Piha-Paul, S. A.; Hall, D. A.; Mclaughlin, M. L. *Tetrahedron Lett.* **1997**, *38*, 4013–4016. (c) Chhabra, S. R.; Mahajan, A.; Chan, W. C. *Tetrahedron Lett.* **1999**, *40*, 4905–4908.
4. (a) Tanaka, K.; Sawanishi, H. *Tetrahedron: Asymmetry* **1998**, *9*, 71–77. (b) Tanaka, K.; Sawanishi, H. *Tetrahedron* **1998**, *54*, 10029–10042.
5. (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. Engl.* **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.
6. 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.
7. Windholz, T. B.; Johnston, D. B. R. *Tetrahedron Lett.* **1967**, 2555–2557.
8. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2550.