Synthesis of Conformationally Defined Glutamic Acid Analogues from Readily Available Diels–Alder Adducts

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New amino acids, (±)-*t*-3,*t*-4-bis(carboxymethyl)-*r*-2-pyrrolidinecarboxylic acid (1d) and (±)-*t*-3a,*t*-6a-perhydro-*r*-1,*t*-4,*t*-6-cyclopenta[*c*]pyrroletricarboxylic acid (2), which possess relatively similar configurations to kainic acid, were synthesized from readily available Diels–Alder adducts.

Key words kainic acid; Diels–Alder adduct; ruthenium tetroxide; Strecker synthesis; cyclic Schiff base; cyanotrimethylsilane

L-Glutamic acid is one of the major excitatory neurotransmitters in the mammalian central nervous system and it is capable of activating at least four receptor subtypes, which were named after three agonists, *N*-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainic acid (KA), and one potent antagonist, L-2-amino-4-phosphonobutanoic acid (AP4).[1] The specific binding of L-glutamic acid to each of these receptors is attributed to its conformational properties, of which the key features may be embodied in the selective agonists and antagonists.

KA, isolated as the active principle of the anthelmintic seaweed *Digenea simplex*, has a 4-substituted *trans*-2-carboxy-3-pyrrolidineacetic acid structure (**1**) which includes an L-glutamic acid moiety in a favorable conformation for binding to the KA receptor.[2] Natural products possessing such a structure, including domoic acid from the seaweed *Chondria armata*[3] and acromelic acids A and B from the poisonous mushroom *Clitocybe acromelalga*,[4] are potent agonists at the same receptor. Although KA and KA-type amino acids are selective and powerful neurotoxins, they have recently become useful agents for neuroscience research on the role of L-glutamic acid in the etiology of neurodegenerative disorders such as Huntington's disease.[5]

A number of structural modifications of KA have been performed with the aim of developing more selective KA agonists and antagonists. The olefinic side chain at the 4-position in the structure of KA appears to be essential for high activity since dihydrokainic acid (**1a**, R = isopropyl) has quite weak activity.[6] However, the 4-carboxylic acid analogue (**1b**, R = COOH) was reported to possess excitatory activity similar to that of KA.[7] Interestingly, the 4-unsubstituted compound (**1c**, R = H) is a NMDA receptor agonist.[8] These findings have prompted us to design new KA-type amino acids having a carboxymethyl group (**1d**, R = CH_2COOH) or its equivalent at the 4-position. In this paper, we describe the synthesis of novel KA-type amino acids, *t*-3,*t*-4-bis(carboxymethyl)-*r*-2-pyrrolidinecarboxylic acid (**1d**) and *t*-3a,*t*-6a-perhydro-*r*-1,*t*-4,*t*-6-cyclopenta[*c*]pyrroletricarboxylic acid (**2**). The latter compound was selected as an analogue of **1d** with a bridged structure to prevent free rotation of the two carboxymethyl groups. As regards the stereochemistry of the pyrrolidine ring in both compounds, 2,3-*trans* and 3,4-*cis* configuration, which mimick those of KA, was adopted.

In order to construct the *cis*-3,4-diacetic acid moiety on the pyrrolidine ring, two pyrrolidine derivatives **3** and **4** carrying a 3,4-*cis*-fused cyclohexene were selected because

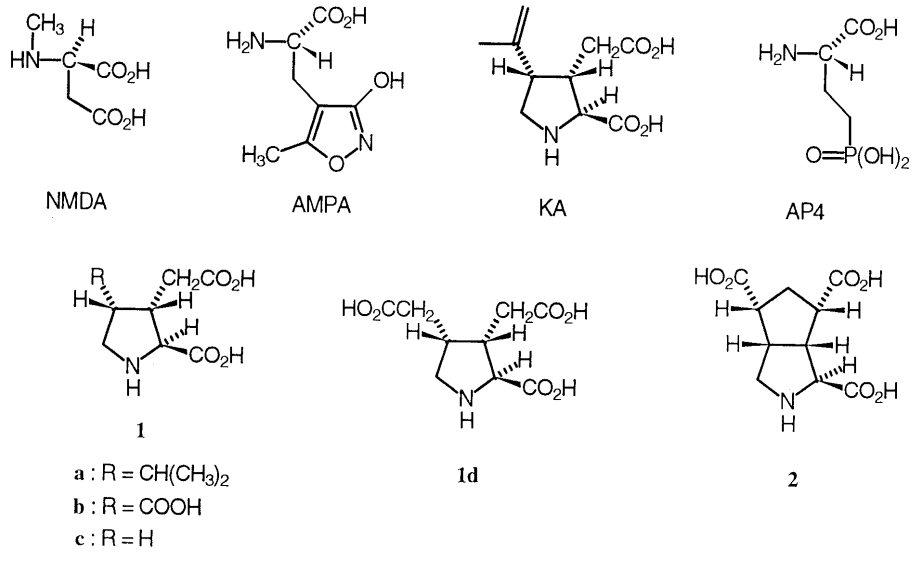

Fig. 1

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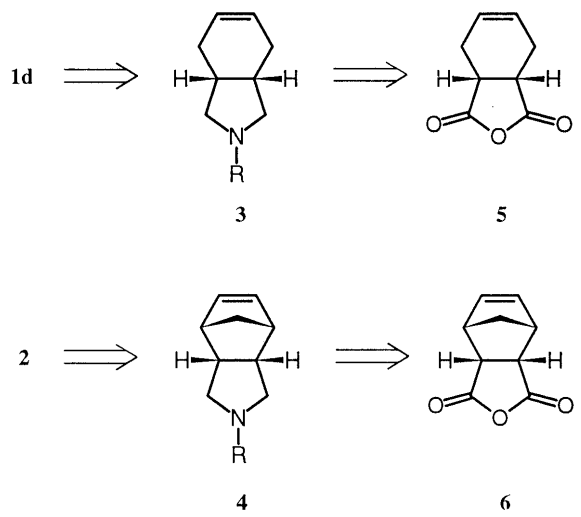


Chart 1

cyclohexene easily affords the 1,6-dicarbonyl relationship upon oxidation. These compounds were to be prepared from the acid anhydrides **5** and **6**, commercially available Diels–Alder adducts, as the starting materials (Chart 1). As for the construction of α-amino acid moiety, we planned to employ the Strecker synthesis.

As shown in Chart 2, the starting acid anhydride **5** was heated with benzylamine[9,10a] to give the imide **7a** in 90% yield. Another starting *endo*-acid anhydride **6** was treated similarly to compound **5** to give the imide **7b** in 85% yield. These imides were reduced by $LiAlH_4$[10] in Et_2O-tetrahydrofuran (THF) to give the pyrrolidine derivatives **8a** and **8b** in 92 and 90% yields, respectively. In order to protect the amine functions of **8a** and **8b**, the *N*-benzyl derivatives **8a** and **8b** were treated with 2,2,2-trichloroethylchloroformate (Troc-Cl)[11] to give the desired compounds **9a** and **9b** in 71 and 73% yields, respectively. At this stage, ring-opening side reactions occurred to afford **10a** and **10b** in 22 and 19% yields.

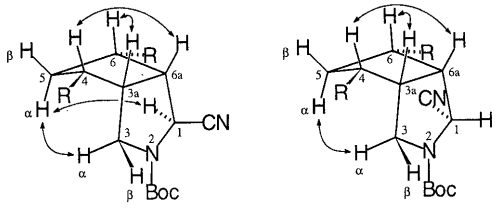
For oxidative cleavage of the double bonds of **9a** and **9b** to obtain dicarboxylic acids, $KMnO_4$ was first employed as an oxidizing agent.[12] Consequently, compound **9a** could be converted into **11a** in the presence of a phase-transfer catalyst (Bu_4NBr) in 72% yield. However, **9b** was not efficiently converted into **11b** under these reaction conditions using any catalyst examined (Bu_4NBr, 18-crown-6, and dicyclohexyl-18-crown-6). So we tried ruthenium tetroxide (RuO_4), a well known versatile oxidizing agent in organic synthesis,[13] which is able to oxidize alcohols, olefins, aromatic rings, *N*-acylamines, *etc.* As a result, chemoselective oxidation of **9b** was accomplished at 0 °C for 8 h without affecting the α-methylene moiety of the nitrogen atom. Thin layer chromatography (TLC) of the reaction mixture showed almost a single spot and no unidentified signal was observed in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the crude product, which includes a trace of RuO_2. The crude **11b** was then esterified without further purification at this stage. Similarly, RuO_4 oxidation of compound **9a** afforded **11a** contaminated with RuO_2, but caused an improvement of the yield of the two steps from **9a** to **12a** (84%).

Esterification[14] of the dicarboxylic acids **11a** and **11b** was carried out as follows. The dicarboxylic acid **11a** was treated with isobutylene (in CH_2Cl_2, H_2SO_4, room temperature, 4 d) to give **12a** in 84% yield, but **11b** was not efficiently esterified under similar conditions (20—30% yield), so employment of both $BF_3 \cdot Et_2O$ and anhydrous *p*-toluenesulfonic acid (TsOH)[15] in place of sulfuric acid in the system was examined and resulted in an improved yield (62% from **9b** to **12b**). Compounds **12a** and **12b** were reduced with zinc in AcOH to remove Troc groups,[11] giving **13a** and **13b** in 70 and 88% yields, respectively.

Cyanation at the α-position of pyrrolidine ring in compounds **13a** and **13b** was accomplished *via* cyclic Schiff bases[16] as follows. Chlorination on the nitrogens of **13a** and **13b** with *N*-chlorosuccinimide (NCS) generated **14a** and **14b** in 90 and 94% yields, respectively. These compounds were treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene to afford the cyclic Schiff bases **15a** and **15b**; they were obtained as benzene solutions which had only been washed with water to remove DBU because of the instability of the products at high concentration. When **13b** was treated under a similar condition, no epimerization was observed on TLC or ^{1}H-NMR. This suggests that **14b** does not isomerize during the conversion into **15b**. The benzene solutions obtained above were treated with cyanotrimethylsilane in the presence of zinc iodide to generate the aminonitriles **16a** and **16b**, which seemed to consist of *cis*-isomers and *trans*-isomers. In the case of **16a**, ^{1}H-NMR showed two kinds of 2-methine proton signals at δ 3.89 and 4.36. Hydrolysis of **16a** in 6 N HCl–AcOH at 100 °C for 6 h gave a mixture of **1d** and **19**, which could not be separated from each other, but the ratio of **1d** and **19** was determined to be 56 : 44 from the ^{1}H-NMR spectrum. Separation of the isomers of **16a** as *N-tert*-butoxycarbonyl (Boc) forms was achieved by fractional recrystallization from diisopropyl ether to give 2,3-*trans*-**17a** and 2,3-*cis*-**18a** in 39 and 34% yields from **14a** (3 steps). The stereochemistry of these compounds was determined from that of the corresponding final amino acids. Although the addition reaction of cyanotrimethylsilane to acyclic Schiff bases has been reported to show high diastereoselectivity,[17] in the case of **15a**, the diastereoselectivity of the cyanation was much lower.

Meanwhile, in the case of **16b**, ^{1}H-NMR showed almost a single isomer. Separation and purification of the product from the reaction mixture were accomplished as the *N-tert*-butoxycarbonyl form by using silica gel column chromatography, to give 1,6a-*trans*-**17b** and 1,6a-*cis*-**18b** in 90 and 0.5% yields from **14b** (3 steps). The structures were determined by NMR analysis as follows. First, the signals of the protons were assigned by two dimensional (2D)-NMR (H–H correlation spectroscopy (COSY) and C–H COSY). In a ^{1}H–^{1}H nuclear Overhauser effect (NOE) experiment (Fig. 2), NOE was observed between 1-H and 5-α-H of **17b**, while for **18b**, no such NOE was observed. As NOEs were also observed between 3-α-H and 5-α-H in both **17b** and **18b**, the relative configurations of 3a-, 4-, 6-, and 6a-H are all *cis*, in view of the other NOE relationships indicated in Fig. 2.

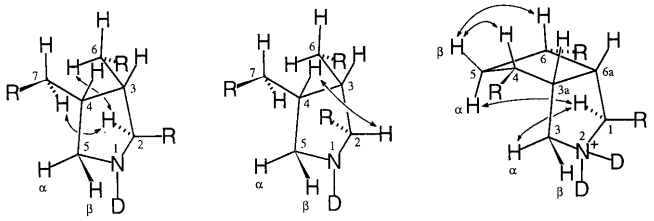
Compound **17a** was heated in 6 N HCl–AcOH at 100 °C



17b' 18b'

R = $CO_2C(CH_3)_3$

Fig. 2. NOE Relationships of Compounds **17b** and **18b**



1d' 19' 2'

R = CO_2D

Fig. 3. NOE Relationships of Compounds **1d**, **19**, and **2**

for 6 h and treated with Dowex 1-X4 (AcO^- form, eluted with 2 N AcOH) to give the target, (±)-*t*-3,*t*-4-bis(carboxymethyl)-*r*-2-pyrrolidinecarboxylic acid (**1d**), in 94% yield (72% after recrystallization from water). Compound **18a** was treated in a similar manner to give (±)-*c*-3,*c*-4-bis(carboxymethyl)-*r*-2-pyrrolidinecarboxylic acid (**19**) in 92% yield (70% after recrystallization from water). The structures of the amino acids **1d** and **19** were determined by NMR analysis (H–H COSY, C–H COSY, NOE). From the NOE data for **1d** (Fig. 3), the proton at the 2-position is near the 6,7-methylene protons but far from the proton at the 4-position. In contrast, from the NOE data for **19**, the proton at the 2-position is near the proton at the 4-position but far from the 6,7-methylene protons.

Compound **17b** was also heated in 6 N HCl–AcOH at 100 °C for 6 h and treated with Dowex 1-X4 (AcO^- form, eluted with 2 N AcOH) to give another target, (±)-*t*-3a,*t*-6a-perhydro-*r*-1,*t*-4,*t*-6-cyclopenta[*c*]pyrroletricarboxylic acid (**2**), in 89% yield (80% after recrystallization from water). The stereochemistry of **2** was confirmed by the NOE relationships between 1- and 3-α-H, 1- and 5-α-H, 4- and 5-β-H, and 5-β- and 6-H (Fig. 3).

In conclusion, we have succeeded in synthesizing the new amino acids **1d** and **2**, which possess relative configurations of 2,3-*trans* (1,6a-*trans*) and 3,4-*cis* (3a,6a-*cis*) similar to those of the KA-type amino acids.

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. NMR spectra were recorded in chloroform-*d* ($CDCl_3$), except for compounds **11a**, **11b**, **1d**, **2**, and **19**, on a GSX-400 spectrometer with tetramethylsilane as an internal standard. Analyses of **11a** and **11b** were done in dimethylsulfoxide-d_6 (DMSO-d_6) with tetramethylsilane as an internal standard. Analyses of **1d**, **2**, and **19** were done in deuterium oxide (D_2O) or 2 N deuterium chloride (DCl) with 1,4-dioxane as an internal standard (δ 3.7 for ^{1}H-NMR and δ 67.4 for ^{13}C-NMR). The ^{1}H–^{1}H NOE experiments in the difference mode were performed at 25 °C for 30—60 mg of sample in 0.6 ml of $CDCl_3$, D_2O, or 2 N DCl. The terms *cis* and *trans* in the assignment of ^{1}H-NMR data were used for the relationships between the corresponding protons and the vicinal methine protons. Infrared (IR) spectra were recorded on a Hitachi 270-30 spectrophotometer. Mass spectra (MS) were obtained with a JEOL JMS-DX300 instrument. TLC was performed on Silica gel 60 F_{254} plates (0.25 mm, Merck). Column chromatography was performed on silica gel (Kieselgel 60, 70—230 mesh, Merck). Flash chromatography was performed on silica gel (Silica gel 60, 230—400 mesh, Nacalai Tesque). The starting materials, *cis*-1,2,3,6-tetrahydrophthalic anhydride (**5**) and *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (**6**), were purchased from Aldrich Chemical Company, Inc. (13,689-1 and 24,763-4).

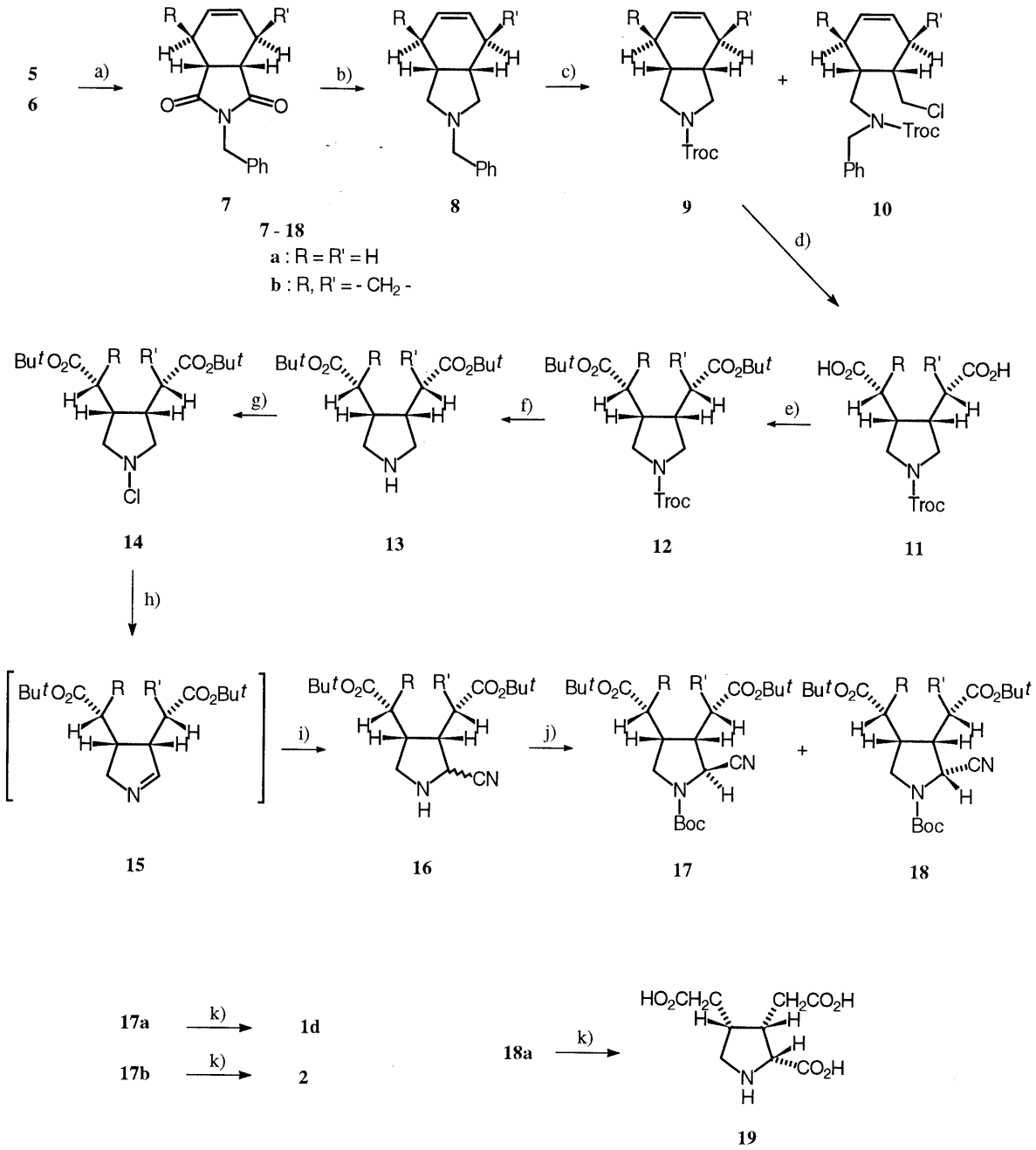
***cis*-2-Benzyl-1,3,3a,4,7,7a-hexahydro-1,3-isoindoledione (7a) (*cis*-8-Benzyl-8-azabicyclo[4.3.0]non-3-ene-7,9-dione)** A mixture of compound **5** (15.2 g, 0.10 mol), benzylamine (10.7 g, 0.10 mol) and EtOH (30 ml) was heated under nitrogen at 165—175 °C for 2 h. The reaction mixture was dissolved in CH_2Cl_2 (300 ml) and the solution was washed with 5% HCl (100 ml), saturated $NaHCO_3$ (100 ml), and water (100 ml), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residual solid was recrystallized from diisopropyl ether to give 21.8 g of **7a** (90%) as colorless needles, mp 87 °C (lit.[9b] mp 87 °C).

2-Benzyl-1,3,*r*-3a,4,7,*c*-7a-hexahydro-*t*-4,*t*-7-methano-1,3-isoindoledione (7b) {(1*R,2*S**,6*R**,7*S**)-4-Benzyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione)}** This compound was obtained as colorless plates, mp 81—82 °C, from **6** in 85% yield in a similar manner to **7a**. ^{1}H-NMR ($CDCl_3$) δ: 1.48—1.52 (1H, m, 8-H), 1.65—1.70 (1H, m, 8-H), 3.21—3.27 (2H, m, 3a-, 7a-H), 3.33—3.37 (2H, m, 4-, 7-H), 4.48 (2H, s, $PhCH_2$), 5.89 (2H, t, J=1.8 Hz, 5-, 6-H), 7.22—7.31 (5H, m, aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 41.91 (t), 44.92 (d), 45.65 (d), 52.03 (t), 127.64 (d), 128.27 (d), 128.80 (d), 134.23 (d), 135.95 (s), 177.28 (s). IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O). MS *m/z*: 253 (M^+). *Anal.* Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.05; H, 6.17; N, 5.46.

***cis*-2-Benzyl-1,3,3a,4,7,7a-hexahydroisoindole (8a) (*cis*-8-Benzyl-8-azabicyclo[4.3.0]non-3-ene)** A solution of **7a** (25.00 g, 0.10 mol) in THF (150 ml) was added dropwise to a suspension of $LiAlH_4$ (8.60 g, 0.10 mol) with stirring under nitrogen at room temperature and the mixture was refluxed for 2 h. It was cooled in an ice bath, then water (10 ml) was added dropwise with vigorous stirring and more water (10 ml) was added at room temperature. The precipitate was filtered off with the aid of Hyflo super-cel (Johns-Manville). The filtrate was concentrated under reduced pressure and the residue was distilled under reduced pressure to give 20.4 g of **8a** (92%) as a colorless oil, bp 113—115 °C (2 mmHg) [lit.[10a] bp 140—160 °C (4 mmHg)].

2-Benzyl-1,3,*r*-3a,4,7,*c*-7a-hexahydro-*t*-4,*t*-7-methanoisoindole (8b) {(1*R,2*S**,6*R**,7*S**)-4-Benzyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene)}** This compound was obtained as a colorless oil, bp 118—120 °C (3.5 mmHg), in 90% yield from **7b** in a similar manner to **8a**. ^{1}H-NMR ($CDCl_3$) δ: 1.51—1.55 (1H, m, 8-H), 1.64—1.69 (1H, m, 8-H), 1.91—1.93 (2H, m, 1-, 3-H), 2.76—2.79 (2H, m, 3a-, 7a-H), 2.79—2.85 (2H, m, 1-, 3-H), 2.87—2.95 (2H, m, 4-, 7-H), 3.52 (2H, s, $PhCH_2$), 6.14 (2H, t, J=1.8 Hz, 5-, 6-H), 7.15—7.31 (5H, m, aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 44.73 (d), 46.51 (d), 53.58 (t), 56.79 (t), 60.51 (t), 126.73 (d), 128.09 (d), 128.77 (d), 137.18 (d), 139.35 (s). MS *m/z*: 225 (M^+). For further analysis, compound **8b** was led to the picrate. Yellow needles (EtOH), mp 139.5—141 °C. *Anal.* Calcd for $C_{22}H_{22}N_4O_7$: C, 58.15; H, 4.88; N, 12.33. Found: C, 58.14; H, 4.89; N, 12.33.

2,2,2-Trichloroethyl *cis*-1,3,3a,4,7,7a-Hexahydro-1-isoindolecarboxylate (9a) (2,2,2-Trichloroethyl *cis*-8-Azabicyclo[4.3.0]non-3-ene-8-carboxylate) A mixture of **5a** (6.17 g, 20.6 mmol) and Troc-Cl (6.56 g, 31.0 mmol) in dry benzene (100 ml) was refluxed for 12 h. The mixture was cooled and, after addition of benzene (100 ml), washed with 5% HCl (100 ml), water (50 ml), saturated $NaHCO_3$ (100 ml) and water (50 ml), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (hexane–benzene, 1 : 1) to give 4.36 g of **9a** (71%) and 1.92 g of **10a** (22%). **9a**: Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.88—1.98 (2H, m, 4-, 7-H), 2.20—2.31 (2H, m, 4-, 7-H), 2.31—2.43 (2H, m, 3a-, 7a-H), 3.23—3.31 (2H, m, 1-, 3-H), 3.49—3.60 (2H, m, 1-, 3-H), 4.74 (2H, s, CCl_3CH_2), 5.66 (2H, s, 5-, 6-H). ^{13}C-NMR ($CDCl_3$) δ: 24.49 (t), 33.38 (d), 34.12 (d), 50.90 (t), 51.52 (t), 74.75 (t), 95.86 (s), 124.11 (d), 124.29 (d), 155.52 (s). IR ν_{max}^{neat} cm^{-1}: 1728 (C=O), 1662 (C=C). MS *m/z*: 297 (M^+), 299 (M^++2), 301 (M^++4). **10a**: Colorless oil. ^{1}H-NMR ($CDCl_3$)



Reagents and conditions: a) $PhCH_2NH_2$, 165-175°C; b) $LiAlH_4$, Et_2O-THF; c) CCl_3CH_2OCOCl, benzene, reflux; d) ($KMnO_4$, Bu_4NBr, benzene, H_2O, r.t.) or (RuO_2, AcOEt, aq $NaIO_4$, 0°C); e) for **11a**, $(CH_3)_2C{=}CH_2$, H_2SO_4, CH_2Cl_2, r.t.; for **11b**, $(CH_3)_2C{=}CH_2$, TsOH, $Et_2O{\cdot}BF_3$, CH_2Cl_2, 0°C; f) Zn, AcOH, 40°C; g) NCS, Et_2O, r.t.; h) DBU, benzene, r.t.; i) $(CH_3)_3SiCN$, ZnI_2, benzene, r.t.; j) Boc_2O, $CHCl_3$, r.t.; k) 6 N HCl-AcOH, 100°C, then Dowex 1-X4, 2 N AcOH.

Chart 2

δ: 1.79—2.66 (6H, m, $C\underline{H}_2CH{=}CHC\underline{H}_2$, 2 × CH), 3.19—3.69 (4H, m, N–CH_2, Cl–CH_2), 4.58 (2H, s, $PhCH_2$), 4.83 (2H, s, CCl_3CH_2), 5.66 (2H, m, C$\underline{H}$ = C$\underline{H}$), 7.33 (5H, s, aromatic H). IR ν_{max}^{neat} cm^{-1}: 1722 (C=O), 1660 (C=C). MS *m/z*: 423 (M^+), 425 (M^++2), 427 (M^++4).

2,2,2-Trichloroethyl 1,3,*r*-3a,4,7,*c*-7a-Hexahydro-*t*-4,*t*-7-methano-2-isoindolecarboxylate (9b) {2,2,2-Trichloroethyl (1*R,2*S**,6*R**,7*S**)-4-Azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-4-carboxylate)}** This compound was obtained as colorless needles (diisopropyl ether–hexane), mp 64.5—66 °C, in 73% yield from **8b**, together with 19% of **10b**, in a similar manner to **9a**. **9b**: ^{1}H-NMR ($CDCl_3$) δ: 1.42 (1H, d, *J*=8.4 Hz, 8-H), 1.55 (1H, d, *J*=8.4 Hz, 8-H), 2.88—2.94 (4H, m, 3a-, 4-, 7-, 7a-H), 3.15—3.24 (2H, m, 1-, 3-H), 3.28—3.39 (2H, m, 1-, 3-H), 4.63, 4.74 (2H, each d, *J*=12.0 Hz, CCl_3CH_2), 6.20 (2H, s, 5-, 6-H). ^{13}C-NMR ($CDCl_3$) δ: 44.60 (d), 45.58 (d), 46.60 (d), 46.65 (d), 48.27 (t), 48.84 (t), 51.77 (t), 74.67 (t), 95.96 (s),135.20 (d), 135.30 (d), 152.10 (s). IR ν_{max}^{KBr} cm^{-1}: 1722 (C=O). MS *m/z*: 309 (M^+), 311 (M^++2), 313 (M^++4). *Anal.* Calcd for $C_{12}H_{14}Cl_3NO_2$: C, 46.40; H, 4.54; N, 4.51. Found: C, 46.60; H, 4.59; N, 4.51. **10b**: Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.09—1.70 (2H, m, CH–C$\underline{H}_2$–CH), 2.26—3.46 (8H, m, 4 × CH, N–CH_2, Cl–CH_2), 4.48—4.99 (4H, m, $PhCH_2$, CCl_3CH_2), 6.03—6.43 (2H, m, C$\underline{H}$ = C$\underline{H}$), 7.28 (5H, s, aromatic H). IR ν_{max}^{neat} cm^{-1}: 1722 (C=O). MS *m/z*: 435 (M^+), 437 (M^++2), 439 (M^++4).

***cis*-1-(2,2,2-Trichloroethoxycarbonyl)-3,4-pyrrolidinediacetic Acid (11a)** Method A: A solution of **9a** (7.33 g, 24.5 mmol) in benzene (73 ml) and a solution of $KMnO_4$ (11.6 g, 73.4 mmol) and Bu_4NBr (1.18 g, 3.7 mmol) in water (125 ml) were mixed and vigorously stirred at room temperature for 2 h. The precipitated MnO_2 was filtered off with suction and the aqueous layer was separated from the filtrate. After having been washed with benzene (100 ml), the aqueous layer was acidified (pH 1) by addition of 2 N HCl and extracted with AcOEt (100 ml × 3). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallized from AcOEt–hexane to give 6.60 g of **11a** (72%) as colorless needles, mp 148.5—149.5 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.00—2.40 (4H, m, 2 × C$\underline{H}_2$CO$_2$H), 2.50—2.70 (2H, m, 3-, 4-H), 3.10—3.30 (2H, m, 2-, 5-H), 3.45—3.64 (2H, m, 2-, 5-H), 4.79, 4.82 (2H, each d, J=12.0 Hz, CCl_3CH_2), 12.27 (2H, s, 2 × CO_2H). ^{13}C-NMR ($CDCl_3$) δ: 32.24 (t), 35.93 (d), 36.66 (d), 49.56 (t), 50.18 (t), 73.76 (t), 96.01 (s), 152.15 (s), 173.33 (s), 173.36 (s). IR ν_{max}^{KBr} cm^{-1}: 3464 (OH), 1714 (C=O). MS *m/z*: 361 (M^+), 363 (M^++2), 365 (M^++4). *Anal.* Calcd for $C_{11}H_{14}Cl_3NO_6$: C, 36.36; H, 3.89; N, 3.78. Found: C, 36.44; H, 3.86; N, 3.86.

Method B: A solution of **9a** (9.60 g, 32.2 mmol) in AcOEt (160 ml), $RuO_2 \cdot xH_2O$ (64 mg) and a 10% aqueous solution of $NaIO_4$ (500 ml) were mixed and vigorously stirred at 0 °C for 8 h. The AcOEt layer was separated and the aqueous layer was extracted with AcOEt (100 ml × 3). Isopropyl alcohol (5 ml) was added to the combined AcOEt layer and the solution was left to stand for 2 h. The precipitated RuO_2 was filtered off and the solution was dried over anhydrous Na_2SO_4, then concentrated under reduced pressure to give quantitatively **11a** (11.67 g), which included a trace of RuO_2 and was used in the next step without further purification.

***r*-3a,*c*-6a-Perhydro-2-(2,2,2-trichloroethoxycarbonyl)-*c*-4,*c*-6-cyclopenta[*c*]pyrroledicarboxylic Acid (11b) {(1*R**,5*S**,6*R**,8*S**)-3-(2,2,2-Trichloroethoxycarbonyl)-3-azabicyclo[3.3.0]octane-6,8-dicarboxylic Acid}** This compound was obtained as colorless needles, mp 203—204 °C, in 60% yield from **9b** in a similar manner to **11a** (method A). ^{1}H-NMR (DMSO-d_6) δ: 1.87—1.95 (1H, m, *cis*-5-H), 2.05 (1H, dt, J=12.1, 12.2 Hz, *trans*-5-H), 2.93—3.61 (8H, m, 1-, 3-, 3a-, 4-, 6-, 6a-H), 4.72, 4.82 (2H, each d, J=12.0 Hz, CCl_3CH_2), 12.53 (2H, s, 2 × CO_2H). ^{13}C-NMR (DMSO-d_6) δ: 28.55 (t), 42.76 (d), 43.74 (d), 45.58 (d), 47.87 (t), 48.75 (t), 73.79 (t), 95.92 (s), 151.57 (s), 173.90 (s). IR ν_{max}^{KBr} cm^{-1}: 1736 (C=O), 1718 (C=O), 1676 (C=O). MS *m/z*: 373 (M^+), 375 (M^++2), 377 (M^++4). *Anal.* Calcd for $C_{12}H_{14}Cl_3NO_6$: C, 38.48; H, 3.76; N, 3.74. Found: C, 38.46; H, 3.75; N, 3.81. By method B, compound **11b** was also obtained in 88% yield from 10.0 g of **9b** (60.4 mmol). It contained a trace of RuO_2 and was used in the next step without further purification.

Di-*tert*-butyl *cis*-1-(2,2,2-Trichloroethoxycarbonyl)-3,4-pyrrolidinediacetate (12a) Isobutylene gas was blown into a mixture of compound **11a** (3.43 g, 9.45 mmol), CH_2Cl_2 (140 ml) and sulfuric acid (0.2 ml) with stirring at −10 °C until the volume had increased by 50 ml. The reaction vessel was made airtight, and the mixture was stirred at room temperature for 4 d. The reaction mixture was poured into saturated $NaHCO_3$ (50 ml) and the aqueous layer was extracted with CH_2Cl_2 (50 ml × 2). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel ($CHCl_3$) and the resulting white solid was recrystallized from diisopropyl ether to give 3.78 g of **12a** (84%) as colorless plates, mp 106.5—107.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (18H, s, 6 × CH_3), 2.13—2.40 (4H, m, 5-, 7-H), 2.68—2.76 (2H, m, 3-, 4-H), 3.24, 3.31 (2H, each dd, J=11.4, 5.5 Hz, *trans*-2-, *trans*-5-H), 3.62, 3.65 (2H, each dd, J=11.4, 6.9 Hz, *cis*-2-, *cis*-5-H), 4.72, 4.75 (2H, each d, J=12.1 Hz, CCl_3CH_2). ^{13}C-NMR ($CDCl_3$) δ: 28.05 (q), 34.23 (t),34.30 (t), 36.81 (d), 37.54 (d), 50.18 (t), 50.50 (t), 74.86 (t), 81.08 (s), 95.76 (s), 152.96 (s), 171.01 (s), 171.13 (s). IR ν_{max}^{KBr} cm^{-1}: 1732 (C=O), 1716 (C=O). MS *m/z*: 473 (M^+), 475 (M^++2), 477 (M^++4). *Anal.* Calcd for $C_{19}H_{30}Cl_3NO_6$: C, 48.06; H, 6.37; N, 2.95. Found: C, 47.99; H, 6.37; N, 2.93.

Di-*tert*-butyl *r*-3a,*c*-6a-Perhydro-2-(2,2,2-trichloroethoxycarbonyl)-*c*-4,*c*-6-cyclopenta[*c*]pyrroledicarboxylate (12b) {Di-tert-butyl (1*R,5*S**,6*R**,8*S**)-3-(2,2,2-Trichloroethoxycarbonyl)-3-azabicyclo[3.3.0]octane-6,8-dicarboxylate}** Isobutylene gas was blown into the mixture of compound **11b** prepared by method B (10.61 g, 28.0 mmol), CH_2Cl_2 (300 ml), anhydrous TsOH (60 mg) and $Et_2O \cdot BF_3$ (0.6 ml) with stirring at −10 °C until the volume had increased by 100 ml. The reaction vessel was made airtight, and the mixture was stirred at room temperature for 4 d. Saturated $NaHCO_3$ was added to the reaction mixture until the pH of the aqueous layer became 7—8 and the CH_2Cl_2 was evaporated under reduced pressure. The residue was extracted with AcOEt (200 ml × 2). The organic layer was washed with water (100 ml), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel ($CHCl_3$) and the resulting white solid was recrystallized from diisopropyl ether to give 9.69 g of **12b** (70% from **11b**, 62% from **9b**) as colorless needles, mp 128—129 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (18H, s, 6 × CH_3), 2.01—2.10 (1H, m, *cis*-5-H), 2.23 (1H, dt, J=12.7, 12.8 Hz, *trans*-5-H), 2.82—2.89 (2H, m, 4-, 6-H), 3.02—3.14 (2H, m, 3a-, 6a-H), 3.22—3.25 (2H, m, 1-, 3-H), 3.66—3.84 (2H, m, 1-, 3-H), 4.66, 4.77 (2H, each d, J=12.0 Hz, CCl_3CH_2). ^{13}C-NMR ($CDCl_3$) δ: 28.07 (q), 28.65 (t), 43.54 (d), 44.37 (d), 47.32 (d), 48.43 (t), 48.84 (t), 74.86 (t), 81.15 (s), 81.21 (s), 95.70 (s), 152.30 (s), 171.71 (s). IR ν_{max}^{KBr} cm^{-1}: 1724 (C=O), 1714 (C=O). MS *m/z*: 485 (M^+), 487 (M^++2), 489 (M^++4). *Anal.* Calcd for $C_{26}H_{30}Cl_3NO_6$: C, 49.34; H, 6.21; N, 2.88. Found: C, 49.54; H, 6.47; N, 2.90.

Di-*tert*-butyl *cis*-3,4-Pyrrolidinediacetate (13a) Zinc dust (2.61 g, 40 mmol) was added to a solution of compound **12a** (2.00 g, 4.2 mmol) in AcOH (26 ml) and the mixture was stirred overnight at room temperature. It was filtered with suction and the filtrate was concentrated under reduced pressure. Saturated $NaHCO_3$ (50 ml) was added to the residue and the whole was extracted with $CHCl_3$ (50 ml × 3). The $CHCl_3$ layer was washed with water (30 ml), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give 0.88 g of crude **13a** (70%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (18H, s, 6 × CH_3), 2.12 (2H, dd, J=15.0, 8.4 Hz, 6-, 7-H), 2.21 (1H, br s, NH), 2.30 (2H, dd, J=15.0, 4.8 Hz, 6-, 7-H), 2.48—2.60 (2H, m, 3-, 4-H), 2.63 (2H, dd, J=10.8, 5.5 Hz, *trans*-2-, *trans*-5-H), 3.17 (2H, dd, J=10.8, 5.9 Hz, *cis*-2-, *cis*-5-H). ^{13}C-NMR ($CDCl_3$) δ: 28.07 (q), 35.15 (t), 38.43 (d), 51.78 (t), 80.51 (s), 172.06 (s). IR ν_{max}^{neat} cm^{-1}: 3352 (NH), 1732 (C=O). MS *m/z*: 299 (M^+). Compound **13a** was led to the acetate for elemental analysis. Colorless needles (benzene), mp 127—129 °C. *Anal.* Calcd for $C_{18}H_{33}NO_6$: C, 60.14; H, 9.25; N, 3.90. Found: C, 60.16; H, 9.06; N, 3.80.

Di-*tert*-butyl *r*-3a,*c*-6a-Perhydro-*c*-4,*c*-6-cyclopenta[*c*]pyrroledicarboxylate (13b) {Di-*tert*-butyl (1*R,5*S**,6*R**,8*S**)-3-Azabicyclo[3.3.0]-octane-6,8-dicarboxylate}** Zinc dust (9.40 g, 144 mmol) and water (6 ml) were added to a solution of compound **12b** (7.00 g, 14.38 mmol) in AcOH (60 ml) and the mixture was stirred overnight at 40 °C. The reaction mixture was filtered with suction and the filtrate was concentrated under reduced pressure. $CHCl_3$ (200 ml) was added to the residue and the insoluble solid was filtered off. The filtrate was concentrated under reduced pressure, water (150 ml) was added to the residue and the solution was washed with benzene (150 ml × 2) and Et_2O (150 ml × 3). $NaHCO_3$ was added to the aqueous solution until the pH reached 8 and the whole was extracted with $CHCl_3$ (150 ml × 2). The $CHCl_3$ layer was washed with water (50 ml), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give 3.95 g of crude **13b** (88%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (18H, s, 6 × CH_3), 1.84 (1H, s, NH), 1.90—1.97 (1H, m, *cis*-5-H), 2.02 (1H, q, J=12.8 Hz, *trans*-5-H), 2.50 (2H, dd, J=11.9, 6.9 Hz, *trans*-1-, *trans*-3-H), 2.72—2.82 (2H, m, 4-, 6-H), 2.82—2.89 (2H, m, 3a-, 6a-H), 3.13 (2H, dd, J=11.9, 7.8 Hz, *cis*-1-, *cis*-3-H). ^{13}C-NMR ($CDCl_3$) δ: 27.92 (q), 27.96 (q), 29.55 (t), 44.90 (d), 46.80 (d), 49.96 (t), 50.49 (d), 50.99 (d), 80.97 (s), 81.82 (s), 120.45 (s), 171.20 (s), 171.50 (s). IR ν_{max}^{KBr} cm^{-1}: 3328 (NH), 1726 (C=O). MS *m/z*: 311 (M^+). Compound **13b** was led to the picrate for elemental analysis. Yellow needles (EtOH), mp 196—198 °C. *Anal.* Calcd for $C_{23}H_{32}N_4O_{11}$: C, 51.11; H, 5.97; N, 10.37. Found: C, 51.26; H, 5.99; N, 10.37.

Di-*tert*-butyl *cis*-1-Chloro-3,4-pyrrolidinediacetate (14a) NCS (0.90 g, 6.74 mmol) was added to a solution of compound **13a** (1.99 g, 6.66 mmol) in Et_2O (25 ml) under argon with shading from light and the mixture was stirred at room temperature. It was washed with 10% aqueous sodium sulfite (25 ml) and water (25 ml), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (benzene) to give 2.00 g of **14a** (90%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (18H, s, 6 × CH_3), 2.18 (2H, dd, J=15.8, 8.8 Hz, 6-, 7-H), 2.34 (2H, dd, J=15.8, 5.1 Hz, 6-, 7-H), 2.78—2.87 (2H, m, 3-, 4-H), 2.88 (2H, dd, J=10.3, 6.9 Hz, *trans*-2-, *trans*-5-H), 3.51 (2H, dd, J=10.3, 7.0 Hz, *cis*-2-, *cis*-5-H). ^{13}C-NMR ($CDCl_3$) δ: 27.70 (q), 35.30 (d), 35.51 (t), 67.59 (t), 80.84 (s), 171.36 (s). IR ν_{max}^{neat} cm^{-1}: 1730 (C=O). MS *m/z*: 333 (M^+).

Di-*tert*-butyl 2-Chloro-*r*-3a,*c*-6a-perhydro-*c*-4,*c*-6-cyclopenta[*c*]pyrrole-

dicarboxylate (14b) {Di-*tert*-butyl (1*R,5*S**,6*R**,8*S**)-3-Chloro-3-azabicyclo[3.3.0]octane-6,8-dicarboxylate}** This compound was obtained as a white solid in 94% yield in a similar manner to **14a**. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (18H, s, $6\times CH_3$), 1.99—2.11 (2H, m, 5-H), 2.63—2.70 (2H, br, *trans*-1-, *trans*-3-H), 2.76—2.84 (2H, m, 4-, 6-H), 3.05—3.12 (2H, br, 3a-, 6a-H), 3.53 (2H, m, *cis*-1-, *cis*-3-H). ^{13}C-NMR ($CDCl_3$) δ: 28.08 (q), 28.17 (t), 42.81 (d), 46.72 (d), 65.46 (t), 80.99 (s), 171.62 (s). IR ν_{max}^{KBr} cm^{-1}: 1728 (C=O). MS *m/z*: 346 ($M^+ + 1$).

***tert*-Butyl *t*-3,*t*-4-Bis(*tert*-butoxycarbonylmethyl)-*r*-2-cyano-1-pyrrolidinecarboxylate (17a) and *tert*-Butyl *c*-3,*c*-4-Bis(*tert*-butoxycarbonylmethyl)-*r*-2-cyano-1-pyrrolidinecarboxylate (18a)** A solution of compound **14a** (1.33 g, 3.98 mmol) in benzene (40 ml) was added dropwise to a solution of DBU (0.67 g, 4.38 mmol) in benzene (20 ml) under argon with shading from light, and the mixture was stirred overnight at room temperature. It was washed with water until the washings were neutral, then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure at 30 °C until the volume became 40 ml. Cyanotrimethylsilane (1.5 ml, 11.9 mmol) and zinc iodide (80 mg, 0.25 mmol) were added to the solution and the whole was stirred at room temperature for 2 d. A mixture of dioxane (10 ml) and water (10 ml) was added to the reaction mixture and stirred at room temperature for 1 h. Benzene (40 ml) was added and the aqueous layer was separated. The benzene layer was washed with water ($20\,ml\times 2$), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual brown oil (**16a**) was dissolved in $CHCl_3$ (6 ml), then Boc_2O (670 mg, 3.07 mmol) was added and the solution was stirred overnight at room temperature. After evaporation of the solvent, the mixture was subjected to column chromatography on silica gel (hexane : AcOEt = 6 : 1) to give a mixture of **17a** and **18a** which had the same *Rf* value on silica gel under any condition examined. The resulting colorless oil was crystallized fractionally and repeatedly from diisopropyl ether to give 0.66 g of **17a** (39%) as colorless prisms, mp 114—116 °C and 0.57 g of **18a** (34%) as colorless needles, mp 110—111 °C. **17a**: ^{1}H-NMR ($CDCl_3$) δ: 1.25—1.70 (27H, m, $9\times CH_3$), 2.12—2.44 (4H, m, 6-, 7-H), 2.90—3.12 (3H, m, 3-,4-, *trans*-5-H), 3.62—3.74 (1H, m, *cis*-5-H), 4.35, 4.39 (1H, each s, 2-H). ^{13}C-NMR ($CDCl_3$) δ: 28.04 (q), 28.29 (q), 32.92 (t), 34.21 (t), 34.31 (t), 36.16 (d), 36.98 (d), 42.70 (d), 43.53 (d), 49.07 (t), 49.52 (t), 51.61 (d), 51.73 (d), 81.34 (s), 81.45 (s), 81.79 (s), 81.88 (s), 118.31 (s), 152.94 (s), 153.57 (s), 169.93 (s), 170.17 (s), 170.28 (s). IR ν_{max}^{KBr} cm^{-1}: 1732 (C=O), 1716 (C=O), 1700 (C=O). MS *m/z*: 424 (M^+). *Anal.* Calcd for $C_{22}H_{36}N_2O_6$: C, 62.24; H, 8.55; N, 6.60. Found: C, 62.19; H, 8.67; N, 6.50. **18a**: ^{1}H-NMR ($CDCl_3$) δ: 1.30—1.60 (27H, m, $9\times CH_3$), 2.32—2.50 (2H, m, 6-, 7-H), 2.50—2.66 (2H, m, 6-, 7-H), 2.70—2.80 (1H, m, 4-H), 2.80—2.95 (1H, m, 3-H), 3.34, 3.41 (1H, each d, J = 11.4 Hz, *trans*-5-H), 3.52 (1H, dd, J = 11.4, 6.2 Hz, *cis*-5-H), 4.71, 4.76 (1H, each d, J = 8.1 Hz, 2-H). ^{13}C-NMR ($CDCl_3$) δ: 28.02 (q), 28.08 (q), 28.32 (q), 33.30 (t), 34.46 (t), 36.29 (d), 37.23 (d), 39.68 (d), 40.42 (d), 50.12 (d), 50.33 (d), 51.17 (t), 51.55 (t), 81.28 (s), 81.72 (s), 81.77 (s), 117.17 (s), 153.16 (s), 153.73 (s), 169.99 (s), 170.25 (s), 170.96 (s), 171.28 (s). IR ν_{max}^{KBr} cm^{-1}: 1736 (C=O), 1720 (C=O). MS *m/z*: 424 (M^+). *Anal.* Calcd for $C_{22}H_{36}N_2O_6$: C, 62.24; H, 8.55; N, 6.60. Found: C, 62.49; H, 8.66; N, 6.65.

Tri-*tert*-butyl *r*-1-Cyano-*t*-3a,*t*-6a-perhydro-2,*t*-4,*t*-6-cyclopenta[*c*]pyrroletricarboxylate (17b) {Tri-*tert*-butyl (1*R,2*S**,5*S**,6*R**,8*S**)-2-Cyano-3-azabicyclo[3.3.0]octane-3,6,8-tricarboxylate} and Tri-*tert*-butyl *r*-1-Cyano-*c*-3a,*c*-6a-perhydro-2,*c*-4,*c*-6-cyclopenta[*c*]pyrroletricarboxylate (18b) {Tri-*tert*-butyl (1*R**,2*R**,5*S**,6*R**,8*S**)-2-Cyano-3-azabicyclo-[3.3.0]octane-3,6,8-tricarboxylate}** A solution of compound **14b** (3.84 g, 11.1 mmol) in benzene (40 ml) was added dropwise to a solution of DBU (6.76 g, 44.4 mmol) in benzene (50 ml) under argon with shading from light and the mixture was stirred for 3 d at room temperature. It was washed with water until the washings were neutral, then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure at 30 °C until the volume became 50 ml. Cyanotrimethylsilane (4.2 ml, 33.3 mmol) and zinc iodide (352 mg, 1.1 mmol) were added, and the whole was stirred at room temperature for 2 d. A mixture of dioxane (15 ml) and water (30 ml) was added, and the reaction mixture was stirred at room temperature for 1 h. Benzene (200 ml) was added and the aqueous layer was separated. The benzene layer was washed with water ($50\,ml\times 2$), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual brown solid (**16b**) was dissolved in $CHCl_3$ (25 ml), then Boc_2O (3.08 g, 14.1 mmol) was added and the solution was stirred overnight at room temperature. After evaporation of the solvent, the residue was subjected to flash chromatography on silica gel (hexane : AcOEt = 6 : 1). Recrystallization of the solid obtained from the former fractions from diisopropyl ether gave 4.35 g (90%) of **17b** as colorless needles, mp 139.5—140.5 °C. Recrystallization of the solid obtained from the latter fractions from diisopropyl ether gave 26 mg (0.5%) of **18b** as colorless needles, mp 172—173 °C. **17b**: ^{1}H-NMR ($CDCl_3$) δ: 1.46, 1.48, 1.49 (27H, each s, $9\times CH_3$), 2.04—2.13 (1H, m, *cis*-5-H), 2.20 (1H, q, J = 12.8 Hz, *trans*-5-H), 2.84—3.01 (2H, m, 4-, 6-H), 3.13—3.22 (1H, m, 3a-H), 3.22—3.31 (1H, m, 6a-H), 3.41—3.48 (1H, m, *trans*-3-H), 3.48—3.59 (1H, m, *cis*-3-H), 4.49 (1H, br s, 1-H). ^{13}C-NMR ($CDCl_3$) δ: 28.02 (q), 28.08 (q), 28.25 (q), 29.34 (t), 43.62 (d), 47.03 (d), 47.23 (d), 48.05 (t), 50.02 (d), 50.60, (d), 81.53 (s), 82.23 (s), 118.92 (s), 152.56 (s), 170.84 (s). IR ν_{max}^{KBr} cm^{-1}: 2240 (CN), 1718 (C=O). MS *m/z*: 436 (M^+). *Anal.* Calcd for $C_{23}H_{36}N_2O_6$: C, 63.28; H, 8.31; N, 6.42. Found: C, 63.30; H, 8.30; N, 6.38. **18b**: ^{1}H-NMR ($CDCl_3$) δ: 1.47, 1.48, 1.51 (27H, each s, $9\times CH_3$), 2.24—2.32 (1H, m, *cis*-5-H), 2.48 (1H, dt, J = 13.2, 13.1 Hz, *trans*-5-H), 2.79—2.98 (2H, m, 4-, 6-H), 2.98—3.05 (1H, m, *trans*-3-H), 3.09—3.30 (2H, m, 3a-, 6a-H), 3.94 (1H, br s, *cis*-3-H), 4.94 (1H, br s, 1-H). ^{13}C-NMR ($CDCl_3$) δ: 28.10 (q), 28.27 (q), 29.15 (t), 42.02 (d), 46.43 (d), 46.89 (d), 47.10 (d), 47.99 (t), 50.59 (d), 81.49 (s), 81.70 (s), 82.27 (s), 117.48 (s), 152.80 (s), 170.95 (s). IR ν_{max}^{KBr} cm^{-1}: 2240 (CN), 1722 (C=O). MS *m/z*: 436 (M^+). *Anal.* Calcd for $C_{23}H_{36}N_2O_6$: C, 63.28; H, 8.31; N, 6.42. Found: C, 63.22; H, 8.36; N, 6.35.

***t*-3,*t*-4-Bis(carboxymethyl)-*r*-2-pyrrolidinecarboxylic Acid (1d)** Compound **17a** (240 mg, 0.57 mmol) was heated in AcOH (5 ml) and 6 N HCl (5 ml) at 100 °C for 6 h. The reaction mixture was concentrated under reduced pressure and the residue was treated with Dowex 1-X4 (AcO^- form), which was eluted with 2 N AcOH. The eluate was concentrated to dryness. A small amount of MeOH was added to the residue and the precipitate was filtered off to give 123 mg of crude **1d** (94% yield) as a white powder, which was recrystallized from water to give colorless needles (94 mg, 72% yield), mp 255—257 °C (dec.). ^{1}H-NMR (D_2O) δ: 2.39 (1H, dd, J = 16.9, 8.8 Hz, 7-H), 2.54 (1H, dd, J = 16.9, 5.9 Hz, 7-H), 2.55 (1H, dd, J = 16.9, 8.0 Hz, 6-H), 2.60 (1H, dd, J = 16.9, 7.0 Hz, 6-H), 2.78—2.97 (2H, m, 3-, 4-H), 3.17 (1H, dd, J = 12.0, 7.3 Hz, *trans*-5-H), 3.63 (1H, dd, J = 12.0, 7.3 Hz, *cis*-5-H), 3.93 (1H, d, J = 6.2 Hz, 2-H). ^{13}C-NMR (D_2O) δ: 32.79 (t), 33.46 (t), 36.91 (d), 42.02 (d), 49.57 (t), 65.11 (d), 173.65 (s), 176.28 (s), 176.54 (s). IR ν_{max}^{KBr} cm^{-1}: 3124 (OH), 2612 (NH_2^+), 1720 (C=O), 1714 (C=O), 1640 (C=O). MS (FAB) *m/z*: 232 ($M^+ + 1$). *Anal.* Calcd for $C_9H_{13}NO_6$: C, 46.75; H, 5.67; N, 6.06. Found: C, 46.73; H, 5.68; N, 6.07.

***c*-3,*c*-4-Bis(carboxymethyl)-*r*-2-pyrrolidinecarboxylic Acid (19)** Compound **18a** was treated similarly to **17a** to give crude **19** (92% yield) as a white powder, which was recrystallized from water to give colorless needles (70%), mp 245 °C (dec.). ^{1}H-NMR (D_2O) δ: 2.40—2.56 (4H, m, 6-, 7-H), 2.86—2.97 (1H, m, 4-H), 3.08—3.17 (1H, m, 3-H), 3.26 (1H, dd, J = 12.1, 8.7 Hz, *trans*-5-H), 3.54 (1H, dd, J = 12.1, 7.7 Hz, *cis*-5-H), 4.25 (1H, d, J = 7.7 Hz, 2-H). ^{13}C-NMR (D_2O) δ: 31.23 (t), 33.17 (t), 37.96 (d), 39.33 (d), 49.04 (t), 64.83 (d), 172.34 (s), 176.43 (s), 176.60 (s). IR ν_{max}^{KBr} cm^{-1}: 3456 (OH), 2630 (NH_2^+), 1728 (C=O), 1702 (C=O), 1562 (C=O). MS (FAB) *m/z*: 232 ($M^+ + 1$). *Anal.* Calcd for $C_9H_{13}NO_6$: C, 46.75; H, 5.67; N, 6.06. Found: C, 46.49; H, 5.70; N, 5.98.

***t*-3a,*t*-6a-Perhydro-*r*-1,*t*-4,*t*-6-cyclopenta[*c*]pyrroletricarboxylic Acid (2) {(1*R**,2*S**,5*S**,6*R**,8*S**)-3-Azabicyclo[3.3.0]octane-2,6,8-tricarboxylic Acid}** Compound **17b** (989 mg, 2.27 mmol) was heated in AcOH (6 ml) and 6 N HCl (15 ml) at 100 °C for 6 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in water (50 ml). The solution was washed with benzene ($50\,ml\times 2$) and 2 N NaOH was added until the pH of the solution became 3. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was treated with Dowex 1-X4 (AcO^- form), which was eluted with 2 N AcOH. The eluate was concentrated to dryness and combined with the precipitate to give crude **2** (492 mg, 89% yield), which was recrystallized from water to give colorless prisms (442 mg, 80% yield), mp 284 °C (dec.). ^{1}H-NMR (2 N DCl) δ: 2.01 (1H, dt, J = 12.7, 12.6 Hz, *trans*-5-H), 2.09—2.18 (1H, m, *cis*-5-H), 2.95—3.10 (3H, m, *trans*-3-, 4-, 6-H), 3.20—3.35 (2H, m, 3a-, 6a-H), 3.56—3.63 (1H, m, *cis*-3-H), 4.27 (1H, d, J = 4.8 Hz, 1-H). ^{13}C-NMR (2 N DCl) δ: 28.32 (t), 41.76 (d), 43.82 (d), 44.04 (d), 45.44 (d), 46.39 (t), 59.87 (d), 168.91 (s), 174.64 (s), 174.84 (s). IR ν_{max}^{KBr} cm^{-1}: 3176 (OH), 3128 (NH_2^+), 1736 (C=O), 1716 (C=O), 1606 (C=O),1566 (C=O). MS (FAB) *m/z*: 244 ($M^+ + 1$). *Anal.* Calcd for $C_{10}H_{13}NO_6$: C, 49.40; H, 5.39; N, 5.76. Found: C, 49.39; H, 5.44; N, 5.77.

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