Stereospecific Synthesis of *cis*-2,4-Pyrrolidinedicarboxylic Acid and *cis*-2,5-Piperidinedicarboxylic Acid

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Lactams derived from hetero Diels–Alder adducts were stereospecifically converted into *cis*-2,4-pyrrolidinedicarboxylic acid and *cis*-2,5-piperidinedicarboxylic acid by ruthenium tetroxide oxidation. Optically active (2*S*,4*S*)-(−)-2,4-pyrrolidinedicarboxylic acid and (2*R*,4*R*)-(+)-2,4-pyrrolidinedicarboxylic acid were synthesized from (1*S*,4*R*)-(+)-2-azabicyclo[2.2.1]hept-5-en-3-one and (1*R*,4*S*)-(−)-2-azabicyclo[2.2.1]hept-5-en-3-one, respectively.

Key words stereospecific synthesis; Diels–Alder adduct; ruthenium tetroxide; *cis*-2,4-pyrrolidinedicarboxylic acid; *cis*-2,5-piperidinedicarboxylic acid; 2-azabicyclo[2.2.1]hept-5-en-3-one

During our studies to obtain new types of amino acids with a *cis*-1,4-dicarboxylic acid relationship by utilizing ruthenium tetroxide oxidation of nitrogen containing Diels–Alder adducts, we have synthesized kainic acid analogs[1] and cyclic hydrazoacetic acids.[2] Here we report the stereospecific synthesis of *cis*-2,4-pyrrolidinedicarboxylic acid (**4**)[3] and *cis*-2,5-piperidinedicarboxylic acid (**8**),[4] which show activities at glutamic acid receptors.

One target, *cis*-2,4-pyrrolidinedicarboxylic acid has been synthesized in racemic form from tetraethyl 1-acetamido-4-hydroxybutane-1,1,3,3-tetracarboxylate,[3a] and in optically active forms from *trans*- and *cis*-4-hydroxy-L-proline.[3b] The former method, which involves cyclization and decarboxylation, affords a mixture of *cis*- and *trans*-isomers. Bridges *et al.* synthesized all four stereoisomers of 2,4-pyrrolidinedicarboxylic acid by the latter method, but the possibility of racemization can not be ruled out, and in fact the absolute values of the specific rotation for the enantiomers of *cis*-2,4-pyrrolidinedicarboxylic acid did not coincide.[3b]

The starting material for *cis*-2,4-pyrrolidinedicarboxylic acid, 2-azabicyclo[2.2.1]hept-5-en-3-one (**1**), which is derived from a Diels–Alder adduct,[5] has recently been utilized for syntheses of carbocyclic nucleosides,[6] and is commercially available in racemic and optically active forms.[7] First, we investigated the most suitable *N*-protecting group among benzoyl (Bz), *tert*-butoxycarbonyl (Boc) and 2,2,2-trichloroethoxycarbonyl (Troc) groups. The lactam **1** was reduced by $LiAlH_4$ to give the amine,[5b] which was not isolated because of its low-boiling and volatile character, but was converted to *N*-protected forms (**2a**: 78%, **2b**: 59%, **2c**: 67%). Compounds **2a**, **2b** and **2c** were oxidized with ruthenium tetroxide (generated *in situ* from ruthenium dioxide with aqueous sodium periodate) in ethyl acetate (AcOEt) at 0 °C to give the *cis*-dicarboxylic acids **3a**, **3b** and **3c** in 96, 82 and 82% yields, respectively. The Boc form **3b** was difficult to purify and was converted with diazomethane into the methyl ester **3b′**. Compounds **3a** and **3b′** were heated with acetic acid and 6 N HCl at 90 °C and desalted with Dowex 1 × 4 (AcO^- form) to give racemic **4** quantitatively, respectively. Treatment of **3c** with zinc in acetic acid (AcOH) at 40 °C gave the same amino acid, but the yield was lower because of the difficulty of separating the target compound from inorganic residues.

On account of better yields, ease of crystallization and ease of UV detection, we decided to adopt the Bz group for synthesis of the optically active amino acids. The starting (+)- and (−)-γ-lactams **1** (>99% ee) were converted into the optically active (−)- and (+)-**2a** in the same manner as described for the racemic compound. The melting points and the absolute values of the specific rotation of the enantiomeric intermediates were identical at each step. The final amino acids, (−)- and (+)-**4** were analyzed by the chiral thin layer chromatography (TLC) and proved not to be mutually contaminated. The optical activities of the amino acids seem to reflect directly those of the starting materials and the specific rotations were greater than those reported by Bridges *et al.*[3b]

It had long been believed that another target, *cis*-2,5-piperidinedicarboxylic acid (**8**) was obtainable stereospecifically by catalytic hydrogenation of 2,5-pyridinedicarboxylic acid, but inconsistent effects of thus obtained **8** on *N*-methyl-D-aspartic acid (NMDA) receptor had been reported; then Madsen *et al.* indicated that the hydrogenation products were mixtures of *cis*- and *trans*-2,5-pyridinedicarboxylic acids.[4a] So, a method for stereospecific or highly stereoselective synthesis of the *cis*- form was still required.

The starting lactam, 2-azabicyclo[2.2.2]oct-5-en-3-one (**5**) was prepared as the racemic form according to the reported method.[5b] Reduction of **5** with $LiAlH_4$ followed by *N*-protection afforded *N*-Bz **6a**, *N*-Boc **6b**, or *N*-Troc **6c** in 68%, 74%, or 70% yield, respectively. Without affecting the α-methylene moiety of the nitrogen atom, these compounds were oxidized with RuO_4 at 0 °C, giving the dicarboxylic acids **7a**, **7b** and **7c** in 91%, 92%, and 96% yields, respectively. Treatments of **7a**—**c** in the same manner as described for the pyrrolidine derivatives **3a**—**c** gave **8**[4a] in almost quantitative yields from **7a** and **7b**, and in lower yield (62%) from **7c**. The ^{1}H-NMR spectra of crude **8** in each case indicated that the products do not contain the *trans*-isomer.

In conclusion, we accomplished the stereospecific synthesis of *cis*-2,4-pyrrolidinedicarboxylic acid and *cis*-2,5-piperidinedicarboxylic acid.

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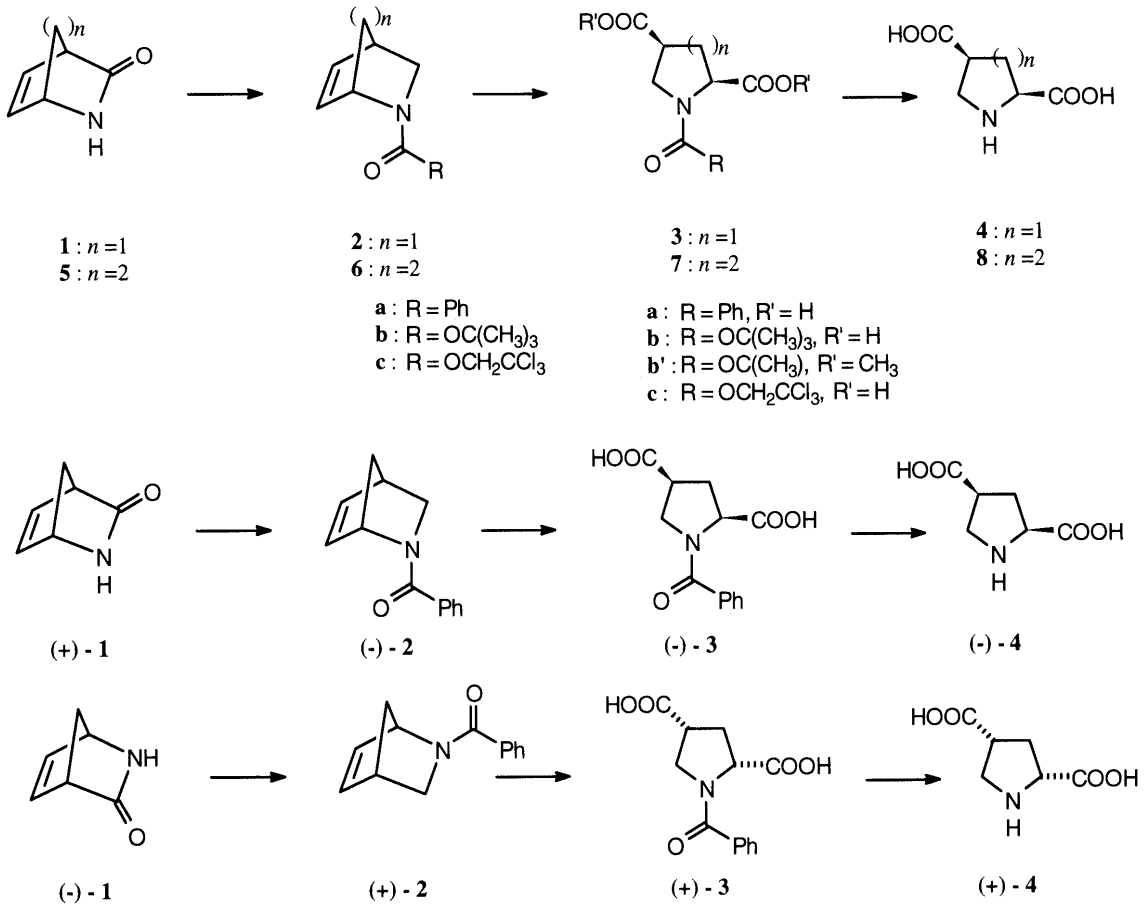

Chart 1

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. NMR spectra were recorded in chloroform-*d* ($CDCl_3$) or methyl alcohol-d_4 with tetramethylsilane as an internal standard, or in deuterium oxide (D_2O) with 1,4-dioxane as an internal standard (δ 3.7 for ^{1}H-NMR and δ 67.4 for ^{13}C-NMR) on a JEOL GSX-400 spectrometer. Infrared (IR) spectra were recorded on a Hitachi 270-30 spectrophotometer. Mass spectra (MS) were obtained with a JEOL JMS-DX300 instrument. Chiral TLC was performed on HPTLC plates CHIR (Merck, Art. 14101). Column chromatography was performed on silica gel (Kieselgel 60, 70—230 mesh, Merck). The optically active starting materials, (1*S*,4*R*)-(+)- and (1*R*,4*S*)-(−)-2-azabicyclo[2.2.1]hept-5-en-3-ones, were purchased from Chiroscience Limited (England).

(±)-2-Benzoyl-2-azabicyclo[2.2.1]hept-5-ene (2a) A solution of the lactam **1** (400 mg, 3.67 mmol) in ether (20 ml) and tetrahydrofuran (THF, 5 ml) were added dropwise to a suspension of $LiAlH_4$ (730 mg, 19.2 mmol) in ether (50 ml) with stirring under nitrogen at room temperature and the mixture was refluxed for 7 h. It was cooled in an ice bath, then water (3 ml) was added dropwise with vigorous stirring. The white precipitate was filtered off with the aid of Hyflo Super-Cel (Johns-Manville). Benzoyl chloride (570 mg, 4.05 mmol) and aqueous sodium carbonate (0.49 g in 10 ml water) were added to the filtrate and the mixture was stirred for 14 h at room temperature. It was extracted with ether (20 ml × 4) and the combined organic layer was washed with water (20 ml × 2), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual yellow oil was subjected to column chromatography on silica gel ($CHCl_3$), giving 568 mg of **2a** (78%) as a white solid, which was recrystallized from diisopropyl ether-hexane to give colorless prisms, mp 65—66°C. ^{1}H-NMR ($CDCl_3$) δ: 1.61—1.70 (2H, m, 7-H), 2.61 (0.4H, d, J=8.8 Hz, 3-H), 2.97 (0.6H, d, J=10.6 Hz, 3-H), 3.22 (0.4H, br s, 4-H), 3.31 (0.6H, br s, 4-H), 3.50—3.62 (1H, m, 3-H), 4.52 (0.6H, s, 1-H), 5.20 (0.4H, s, 1-H), 6.27 (1H, m, 5-H), 6.41 (0.6H, d, J=2.2 Hz, 6-H), 6.55 (0.4H, d, J=5.1 Hz, 6-H), 7.30—7.55 (5H, m, aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 42.46 (d), 43.75 (d), 45.69 (t), 47.39 (t), 48.97 (t), 49.54 (t), 60.28 (d), 63.78 (d), 127.08 (d), 127.19 (d), 127.35 (d), 128.19 (d), 128.35 (d), 129.77 (d), 130.07 (d), 133.23 (d), 135.59 (d), 136.46 (s), 137.16 (s), 138.24 (d), 169.22 (s), 171.02 (s). IR ν_{max}^{KBr} cm^{-1}: 1614 (C=O). MS *m/z*: 199 (M^+). *Anal.* Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.22; H, 6.74; N, 7.02.

***tert*-Butyl (±)-2-Azabicyclo[2.2.1]hept-5-ene-2-carboxylate (2b)** A solution of the lactam **1** (400 mg, 3.67 mmol) in ether (20 ml) and THF (5 ml) was added dropwise to a suspension of $LiAlH_4$ (730 mg, 19.2 mmol) in ether with stirring under nitrogen at room temperature and the mixture was refluxed for 7 h. It was cooled in an ice bath, then water (3 ml) was added dropwise with vigorous stirring. The white precipitate was filtered off with the aid of Hyflo Super-Cel (Johns-Manville). Di-*tert*-butyl dicarbonate (890 mg, 4.08 mmol) was added to the filtrate and the mixture was stirred for 14 h at room temperature. After addition of benzene (80 ml), the mixture was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual pale yellow oil was subjected to column chromatography on silica gel (hexane : AcOEt = 9 : 1), giving 420 mg of **2b** (59%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s, CH_3 × 3), 1.51—1.60 (2H, m, 7-H), 2.55—2.71 (1H, m, 3-H), 3.16 (1H, s, 4-H), 3.30 (1H, dd, J=9.2, 2.9 Hz, 3-H), 4.57, 4.71 (1H, each s, 1-H), 6.27, 6.38 (2H, each s, –HC=CH–). ^{13}C-NMR ($CDCl_3$) δ: 28.52 (q), 42.99 (d), 43.49 (d), 45.96 (t), 46.31 (t), 48.10 (t), 59.97 (d), 61.17 (d), 79.07 (s), 133.79 (d), 134.46 (d), 136.11 (d), 155.95 (s). IR ν_{max}^{neat} cm^{-1}: 1700 (C=O). MS *m/z*: 195 (M^+).

2,2,2-Trichloroethyl (±)-2-Azabicyclo[2.2.1]hept-5-ene-2-carboxylate (2c) A solution of the lactam **1** (400 mg, 3.67 mmol) in ether (20 ml) and THF (5 ml) was added dropwise to a suspension of $LiAlH_4$ (730 mg, 19.2 mmol) in ether (50 ml) with stirring under nitrogen at room temperature and the mixture was refluxed for 7 h. It was cooled in an ice bath, then water (3 ml) was added dropwise with vigorous stirring. The white precipitate was filtered off with the aid of Hyflo Super-Cel (Johns-Manville). 2,2,2-Trichloroethoxycarbonyl chloride (854 mg, 4.03 mmol) and aqueous sodium carbonate (0.49 g in 10 ml of water) were added to the filtrate and the mixture was stirred for 18 h at room temperature. It was extracted with ether (20 ml × 4) and the combined organic layer was washed with water (20 ml × 2), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual pale yellow oil was subjected to column chromatography on silica gel (hexane : AcOEt =

9 : 1), giving 660 mg of **2c** (67%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.58—1.70 (2H, m, 7-H), 2.70—2.83 (1H, m, 3-H), 3.25 (1H, s, 4-H), 3.37—3.52 (1H, m, 3-H), 4.62—4.82 (3H, m, OCH_2CCl_3, 1-H), 6.28—6.44 (2H, m, –HC=CH–). ^{13}C-NMR ($CDCl_3$) δ: 42.93 (d), 43.38 (d), 46.13 (t), 46.45 (t), 48.13 (t), 48.27 (t), 60.97 (d), 61.49 (d), 74.65 (t), 95.87 (s), 134.03 (d), 134.23 (d), 137.05 (d), 137.33 (d), 153.76 (s), 153.93 (s). IR ν_{max}^{near} cm^{-1}: 1704 (C=O). MS *m/z*: 269 (M^+), 271 (M^++2), 273 (M^++4).

(±)-*cis*-1-Benzoyl-2,4-pyrrolidinedicarboxylic Acid (3a) A solution of **2a** (150 mg, 0.753 mmol) in AcOEt (9 ml), $RuO_2 \cdot xH_2O$ (6 mg) and a 10% $NaIO_4$ solution (18 ml) were mixed and the whole was vigorously stirred at 0 °C for 8 h. The AcOEt layer was separated and the aqueous layer was extracted with AcOEt (10 ml × 4). Isopropyl alcohol (1 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, giving 192 mg of **3a** (97%) as a white solid, which was recrystallized from AcOEt–hexane to afford colorless prisms, mp 160.5—161.5 °C. ^{1}H-NMR (CD_3OD) δ: 2.26 (1H, ddd, J=12.8, 8.8, 8.4 Hz, 3-H), 2.70 (1H, dt, J=12.8, 8.1 Hz, 3-H), 3.11—3.24 (1H, m, 4-H), 3.74 (1H, dd, J=10.6, 7.7 Hz, 5-H), 3.87 (1H, dd, J=10.6, 9.2 Hz, 5-H), 4.65 (1H, t, J=8.4 Hz, 2-H), 7.40—7.62 (5H, m, aromatic H). ^{13}C-NMR (CD_3OD) δ: 33.23 (t), 44.23 (d), 53.13 (t), 60.37 (d), 128.34 (d), 129.63 (d), 131.83 (d), 136.99 (s), 171.93 (s), 174.57 (s), 174.91 (s). IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 1720 (C=O). MS *m/z*: 263 (M^+). *Anal.* Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.28; H, 4.86; N, 5.31.

Dimethyl (±)-*cis*-1-*tert*-Butoxycarbonyl-2,4-pyrrolidinedicarboxylate (3b′) A solution of **2b** (100 mg, 0.512 mmol) in AcOEt (4 ml), $RuO_2 \cdot xH_2O$ (4 mg) and a 10% $NaIO_4$ solution (12 ml) were mixed and the whole was vigorously stirred at 0 °C for 8 h. The AcOEt layer was separated and the aqueous layer was extracted with AcOEt (10 ml × 4). Isopropyl alcohol (0.5 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. The residual black oil was dissolved in MeOH (1 ml) and treated with diazomethane. The solution was concentrated and the residue was subjected to column chromatography on silica gel (hexane : AcOEt = 2 : 1) to give 121 mg of **3b′** (82%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.41 and 1.45 (9H, each s, $C(CH_3)_3$), 2.25—2.39 (1H, m, 3-H), 2.45—2.57 (1H, m, 3-H), 3.03—3.12 (1H, m, 4-H), 3.69 (3H, s, $COOCH_3$), 3.72 (3H, s, $COOCH_3$), 3.75—3.86 (2H, m, 5-H), 4.23—4.40 (1H, m, 2-H). ^{13}C-NMR ($CDCl_3$) δ: 28.25 (q), 28.37 (q), 32.12 (t), 33.09 (t), 41.64 (d), 42.41 (d), 48.42 (t), 48.66 (t), 52.08 (q), 52.23 (q), 58.39 (d), 58.79 (d), 80.37 (s), 153.99 (s), 157.37 (s), 172.28 (s), 172.56 (s), 172.81 (s). IR ν_{max}^{neat} cm^{-1}: 1746 (C=O), 1706 (C=O). MS *m/z*: 287 (M^+).

(±)-*cis*-1-(2,2,2-Trichloroethoxycarbonyl)-2,4-pyrrolidinedicarboxylic Acid (3c) A solution of **2c** (195 mg, 0.721 mmol) in AcOEt (9 ml), $RuO_2 \cdot xH_2O$ (6 mg) and a 10% $NaIO_4$ solution (18 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 (10 ml × 4). Isopropyl alcohol (1 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. The residual black oil was subjected to column chromatography on silica gel (AcOEt) to give 197 mg of **3c** (82%) as a white solid, which was recrystallized from AcOEt–hexane to afford colorless needles, mp 154—156 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.52—2.66 (2H, m, 3-H), 3.18—3.27 (1H, m, 4-H), 3.85—4.07 (2H, m, 5-H), 4.48—4.55 (1H, m, 2-H), 4.66—4.87 (2H, m, OCH_2CCl_3). ^{13}C-NMR ($CDCl_3$) δ: 31.68 (t), 32.59 (t), 41.30 (d), 42.06 (d), 48.38 (t), 48.91 (t), 58.27 (d), 58.64 (d), 75.14 (t), 75.26 (t), 94.98 (s), 95.17 (s), 152.28 (s), 153.11 (s), 176.41 (s), 177.06 (s), 177.25 (s), 177.28 (s). IR ν_{max}^{KBr} cm^{-1}: 3040 (OH), 1732 (C=O), 1716 (C=O). MS *m/z*: 333 (M^+), 335 (M^++2), 337 (M^++4). *Anal.* Calcd for $C_9H_{10}Cl_3NO_6$: C, 32.31; H, 3.01; N, 4.19. Found: C, 32.48; H, 2.86; N, 4.25.

(±)-*cis*-2,4-Pyrrolidinedicarboxylic Acid (4) From **3a**: The dicarboxylic acid **3a** (130 mg, 0.494 mmol) was heated in AcOH (4 ml) and 6 N HCl (4 ml) at 90 °C for 18 h. Water (10 ml) was added to the reaction mixture and the solution was washed with CH_2Cl_2 (10 ml × 3). The aqueous layer was concentrated under reduced pressure and the residue was treated with Dowex 1 × 4 (AcO^- form), which was eluted with 2 N AcOH. The eluate was concentrated under reduced pressure to give 79 mg of the amino acid **4** (100%) as a white solid, which was recrystallized from aqueous EtOH to afford colorless prisms, mp 226—230 °C. ^{1}H-NMR (D_2O) δ: 2.27 (1H, dt, J=13.9, 7.0 Hz, 3-H), 2.55 (1H, dt, J=13.9, 8.8 Hz, 3-H), 3.25 (1H, m, 4-H), 3.43 (1H, dd, J=12.1, 8.4 Hz, 5-H), 3.55 (1H, dd, J=12.1, 6.2 Hz, 5-H), 4.25 (1H, dd, J=8.8, 7.0 Hz, 2-H). ^{13}C-NMR (D_2O) δ: 32.06 (t), 42.54 (d), 48.14 (t), 60.93 (d), 172.65 (s), 175.90 (s). IR ν_{max}^{KBr} cm^{-1}: 3100 (NH), 1696 (C=O), 1604 (C=O). MS (FAB) *m/z*: 160 (M^++1). *Anal.* Calcd for $C_6H_9NO_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.16; H, 5.81; N, 8.80.

From **3b′**: The ester **3b′** was treated in a similar manner to **3a**, giving **4** quantitatively.

From **3c**: Zinc dust (260 mg, 3.98 mmol) was added to a solution of **3c** (152 mg, 0.454 mmol) in AcOH (3 ml) and the mixture was stirred at room temperature for 18 h and at 40 °C for 6 h. It was filtered with suction and the filtrate was concentrated under reduced pressure. The residue was treated with Dowex 1 × 4 (AcO^- form), which was eluted with 2 N AcOH. The eluate was concentrated under reduced pressure to give 48 mg of the amino acid **4** (66%).

(1*S*,4*R*)-2-Benzoyl-2-azabicyclo[2.2.1]hept-5-ene {(−)-2a} This compound was obtained as colorless prisms (diisopropyl ether–hexane), mp 100.5—101 °C, from (+)-2-azabicyclo[2.2.1]hept-5-en-3-one {(+)-**1**} in a similar manner to that described for racemic **2a**. $[\alpha]_D^{20}$ −150.3° (c=1.01, $CHCl_3$).

(2*S*,4*S*)-1-Benzoyl-2,4-pyrrolidinedicarboxylic Acid {(−)-3a} This compound was obtained as colorless prisms (AcOEt–hexane), mp 164—165 °C, from (−)-**2a** in a similar manner to that described for racemic **3a**. $[\alpha]_D^{24}$ −82.1° (c=1.01, EtOH).

(2*S*,4*S*)-2,4-Pyrrolidinedicarboxylic Acid {(−)-4} This compound was obtained as colorless prisms (70% EtOH), mp 231—233 °C, from (−)-**3a** in a similar manner to that described for racemic **4**. $[\alpha]_D^{21}$ −41.5° (c=1.01, H_2O) {lit.[3b] $[\alpha]_D^{25}$ −40° (c=1.02, H_2O)}.

(1*R*,4*S*)-2-Benzoyl-2-azabicyclo[2.2.1]hept-5-ene {(+)-2a} This compound was obtained as colorless prisms (diisopropyl ether–hexane), mp 100.5—101 °C, from (−)-2-azabicyclo[2.2.1]hept-5-en-3-one {(−)-**1**} in a similar manner to that described for racemic **2a**. $[\alpha]_D^{22}$ +150.3° (c=1.02, $CHCl_3$).

(2*R*,4*R*)-1-Benzoyl-2,4-pyrrolidinedicarboxylic Acid {(+)-3a} This compound was obtained as colorless prisms (AcOEt–hexane), mp 164—165 °C, from (+)-**2a** in a similar manner to that described for racemic **3a**. $[\alpha]_D^{20}$ +82.0° (c=1.04, EtOH).

(2*R*,4*R*)-2,4-Pyrrolidinedicarboxylic Acid {(+)-4} This compound was obtained as colorless prisms (70% EtOH), mp 231—233 °C, from (+)-**3a** in a similar manner to that described for racemic **4**. $[\alpha]_D^{21}$ +41.5° (c=1.01, H_2O) {lit.[3b] $[\alpha]_D^{24}$ +37° (c=1.01, H_2O)}.

(±)-2-Benzoyl-2-azabicyclo[2.2.2]oct-5-ene (6a) A solution of the lactam **5** (420 mg, 3.41 mmol) in ether (20 ml) and THF (5 ml) was added dropwise to a suspension of $LiAlH_4$ (678 mg, 17.9 mmol) in ether (50 ml) with stirring under nitrogen at room temperature and the mixture was refluxed for 7 h. It was cooled in an ice bath, then water (3 ml) was added dropwise with vigorous stirring. The resultant white precipitate was filtered off with the aid of Hyflo Super-Cel (Johns-Manville). Benzoyl chloride (530 mg, 3.77 mmol) and aqueous sodium carbonate (0.48 g in 10 ml water) were added to the filtrate and the mixture was stirred for 14 h at room temperature. It was extracted with ether (20 ml × 4) and the combined organic layer was washed with water (20 ml × 2), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual yellow oil was subjected to column chromatography on silica gel (benzene then AcOEt), giving 495 mg of **6a** (68%) as a white solid, which was recrystallized from AcOEt–hexane to afford colorless prisms, mp 64—64.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.30—1.50 (2H, m, 8-H), 1.60—1.78 (1H, m, 7-H), 1.92—2.13 (1H, m, 7-H), 2.68, 2.69 (1H, each br s, 4-H), 2.97 (0.25H, d, J=9.9 Hz, 3-H), 3.28 (0.75H, each ddd, J=11.7, 2.9, 2.6 Hz, 3-H), 3.48 (1H, dd, J=11.7, 1.8 Hz, 3-H), 4.31 (0.75H, t, J=2.9 Hz, 1-H), 5.31 (0.25H, s, 1-H), 6.25—6.56 (2H, m, –HC=CH–), 7.28—7.45 (5H, m, aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 22.12 (t), 22.16 (t), 25.91 (t), 27.22 (t), 30.33 (d), 30.94 (d), 44.08 (d), 47.75 (t), 49.32 (d), 51.53 (t), 126.75 (d), 126.82 (d), 128.31 (d), 128.45 (d), 129.39 (d), 129.46 (d), 131.42 (d), 133.03 (d), 134.15 (d), 135.03 (d), 136.84 (s), 137.25 (s), 169.58 (s), 170.46 (s). IR ν_{max}^{KBr} cm^{-1}: 1614 (C=O). MS *m/z*: 213 (M^+). *Anal.* Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.75; H, 7.18; N, 6.54.

***tert*-Butyl (±)-2-Azabicyclo[2.2.2]oct-5-ene-2-carboxylate (6b)** A solution of the lactam **5** (420 mg, 3.41 mmol) in ether (20 ml) and THF (5 ml) was added dropwise to a suspension of $LiAlH_4$ (678 mg, 17.9 mmol) in ether (50 ml) with stirring under nitrogen at room temperature

and the mixture was refluxed for 7 h. It was cooled in an ice bath, then water (3 ml) was added dropwise with vigorous stirring. The resultant white precipitate was filtered off with the aid of Hyflo Super-Cel (Johns-Manville). Di-*tert*-butyl dicarbonate (817 mg, 3.74 mmol) was added to the filtrate and the mixture was stirred for 14 h at room temperature. After addition of benzene (80 ml), the mixture was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual pale yellow oil was subjected to column chromatography on silica gel (hexane, then benzene), giving 526 mg of **6b** (74%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.25—1.55 (11H, m, 8-H and $C(CH_3)_3$), 1.55—1.70 (1H, m, 7-H), 1.89—2.01 (1H, m, 7-H), 2.64—2.75 (1H, m, 4-H), 2.88—2.98 (1H, m, 3-H), 3.22 (1H, dd, J=10.3, 2.2 Hz, 3-H), 4.56, 4.71 (1H, each s, 1-H), 6.30—6.48 (2H, m, –HC=CH–). ^{13}C-NMR ($CDCl_3$) δ: 21.96 (t), 22.03 (t), 26.76 (t), 26.96 (t), 28.57 (q), 30.50 (d), 30.74 (d), 44.63 (d), 46.04 (d), 47.88 (t), 48.29 (t), 78.93 (s), 79.02 (s), 132.41 (d), 133.11 (d), 133.62 (d), 134.08 (d), 154.60 (s), 154.89 (s). IR ν_{max}^{KBr} cm^{-1}: 1696 (C=O). MS *m/z*: 209 (M^+).

2,2,2-Trichloroethyl (±)-2-Azabicyclo[2.2.2]oct-5-ene-2-carboxylate (6c) A solution of the lactam **5** (420 mg, 3.41 mmol) in ether (20 ml) and THF (5 ml) was added dropwise to a suspension of $LiAlH_4$ (678 mg, 17.9 mmol) in ether (50 ml) with stirring under nitrogen at room temperature and the mixture was refluxed for 7 h. It was cooled in an ice bath, then water (3 ml) was added dropwise with vigorous stirring. The white precipitate was filtered off with the aid of Hyflo Super-Cel (Johns-Manville). 2,2,2-Trichloroethoxycarbonyl chloride (800 mg, 3.81 mmol) and aqueous sodium carbonate (0.48 g in 10 ml of water) were added to the filtrate and the mixture was stirred for 14h at room temperature. It was extracted with ether (20 ml × 4) and the combined organic layer was washed with water (20 ml × 2), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual yellow oil was subjected to column chromatography on silica gel ($CHCl_3$), giving 679 mg of **6c** (70%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.36—1.48 (2H, m, 8-H), 1.59—1.62 (1H, m, 7-H), 1.94—2.07 (1H, m, 7-H), 2.74—2.83 (1H, m, 4-H), 3.05, 3.11 (1H, each dt, J=10.6, 2.6 Hz, 3-H), 3.33, 3.41 (1H, each dd, J=10.3, 2.2 Hz, 3-H), 4.67—4.81 (3H, m, 2-H, OCH_2CCl_3), 6.38—6.48 (2H, m, –HC=CH–). ^{13}C-NMR ($CDCl_3$) δ: 21.74 (t), 26.52 (t), 26.81 (t), 30.19 (d), 30.37 (d), 45.89 (d), 46.27 (d), 48.00 (t), 48.54 (t), 74.82 (t), 95.90 (s), 95.93 (s), 132.01 (d), 132.44 (d), 134.06 (d), 134.38 (d), 152.97 (s), 153.45 (s). IR ν_{max}^{KBr} cm^{-1}: 1724 (C=O). MS *m/z*: 283 (M^+), 285 (M^++2), 287 (M^++4).

(±)-*cis*-1-Benzoyl-2,5-piperidinedicarboxylic Acid (7a) A solution of **6a** (120 mg, 0.563 mmol) in AcOEt (8 ml), $RuO_2 \cdot xH_2O$ (4 mg) and a 10% $NaIO_4$ solution (14 ml) were mixed and the whole was vigorously stirred at 0 °C for 8 h. The AcOEt layer was separated and the aqueous layer was extracted with AcOEt (10 ml × 4). Isopropyl alcohol (1 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 142 mg of **3a** (91%) as a white solid, which was recrystallized from $CHCl_3$–AcOEt to afford colorless prisms, mp 146—148 °C. ^{1}H-NMR (CD_3OD) δ: 1.44—1.61 (1H, m, 4-H), 1.67—1.92 (1H, m, 4-H), 2.04—2.16 (1H, m, 3-H), 2.26 (0.4H, d, J=11.7 Hz, 3-H), 2.44 (0.6H, dd, J=14.1, 2.0 Hz, 3-H), 2.48—2.60 (1H, m, 5-H), 2.95, 3.28 (1H, each t, J=13.0 Hz, 6-H), 3.85 (0.6H, dd, J=13.6, 4.0 Hz, 6-H), 4.43 (0.4H, d, J=4.4 Hz, 2-H), 4.80 (0.4H, d, J=13.6 Hz, 6-H), 5.39 (0.6H, d, J=5.5 Hz, 2-H), 7.35—7.52 (5H, m, aromatic H). ^{13}C-NMR (CD_3OD) δ: 25.65 (t), 26.65 (t), 27.26 (t), 41.93 (d), 42.38 (d), 42.38 (t), 48.15 (t), 53.07 (d), 59.17 (d), 127.49 (d), 127.81 (d), 129.83 (d), 129.92 (d), 131.25 (d), 136.64 (s), 136.85 (s), 173.15 (s), 173.45 (s), 173.88 (s), 174.15 (s), 175.85 (s), 176.34 (s). IR ν_{max}^{KBr} cm^{-1}: 3464 (OH), 3072 (OH), 1732 (C=O). MS *m/z*: 277 (M^+). *Anal.* Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.68; H, 5.44; N, 5.13.

(±)-*cis*-1-*tert*-Butoxycarbonyl-2,5-piperidinedicarboxylic Acid (7b) A solution of **6b** (255 mg, 1.22 mmol) in AcOEt (17 ml), $RuO_2 \cdot xH_2O$ (9 mg) and a 10% $NaIO_4$ solution (30 ml) were mixed and the whole was vigorously stirred at 0 °C for 8 h. The AcOEt layer was separated and the aqueous layer was extracted with AcOEt (20 ml × 4). Isopropyl alcohol (2 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 305 mg of **3a** (92%) as a pale pink solid, which was recrystallized from AcOEt–hexane to afford colorless prisms, mp 158—160 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.25—1.82 (11H, m, 4-H, $C(CH_3)_3$), 2.02—2.20 (1H, m, 3-H), 2.25—2.40 (1H, m, 3-H), 2.40—2.59 (1H, m, 5-H), 2.87—3.12 (1H, m, 6-H), 4.15—4.40 (1H, m, 6-H), 4.81, 5.01 (1H, each d, J=4.0 Hz, 2-H), 11.53 (2H, br s, COOH). ^{13}C-NMR ($CDCl_3$) δ: 23.86 (t), 24.04 (t), 25.49 (t), 25.67 (t), 28.25 (q), 28.31 (q), 40.68 (d), 40.86 (d), 41.85 (t), 42.85 (t), 52.81 (d), 53.96 (d), 81.13 (s), 81.21 (s), 155.10 (s), 155.68 (s), 177.47 (s), 179.04 (s), 179.20 (s). IR ν_{max}^{KBr} cm^{-1}: 1734 (C=O), 1714 (C=O), 1652 (C=O). MS *m/z*: 273 (M^+). *Anal.* Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.89; H, 7.06; N, 5.22.

(±)-*cis*-1-(2,2,2-Trichloroethoxycarbonyl)-2,5-piperidinedicarboxylic Acid (7c) A solution of **6b** (133 mg, 0.467 mmol) in AcOEt (6 ml), $RuO_2 \cdot xH_2O$ (4 mg) and a 10% $NaIO_4$ solution (12 ml) were mixed and the whole was vigorously stirred at 0 °C for 8 h. The AcOEt layer was separated and the aqueous layer was extracted with AcOEt (10 ml × 4). Isopropyl alcohol (1 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. The residual black oil was subjected to column chromatography on silica gel (AcOEt) to give 156 mg of **7c** (96%) as a white solid, which was recrystallized from AcOEt–hexane to afford colorless plates, mp 160—161 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.48—1.62 (1H, m, 4-H), 1.75—1.90 (1H, m, 4-H), 2.10—2.21 (1H, m, 3-H), 2.36—2.49 (1H, m, 3-H), 2.50—2.61 (1H, m, 5-H), 3.06—3.26 (1H, m, 6-H), 4.35—4.45 (1H, m, 6-H), 4.71—4.90 (2H, m, OCH_2CCl_3), 5.00, 5.03 (each d, J=4.8 Hz, 2-H), 8.92 (2H, br s, COOH). ^{13}C-NMR ($CDCl_3$) δ: 23.69 (t), 23.91 (t), 25.49 (t), 25.77 (t), 40.45 (d), 40.63 (d), 42.71 (t), 42.79 (t), 53.80 (d), 53.86 (d), 75.36 (t), 75.46 (t), 95.13 (s), 95.17 (s), 153.96 (s), 154.61 (s), 176.47 (s), 176.52 (s), 178.52 (s), 178.61 (s). IR ν_{max}^{KBr} cm^{-1}: 3600—2500 (OH), 1712 (C=O). MS *m/z*: 347 (M^+), 349 (M^++2), 351 (M^++4). *Anal.* Calcd for $C_{10}H_{12}Cl_3NO_6$: C, 34.46; H, 3.47; N, 4.02. Found: C, 34.58; H, 3.45; N, 4.07.

(±)-*cis*-2,5-Piperidinedicarboxylic Acid (8) From **7a**: The dicarboxylic acid **7a** (85 mg, 0.307 mmol) was heated in AcOH (3 ml) and 6 N HCl (3 ml) at 90 °C for 18 h. Water (10 ml) was added to the reaction mixture and the solution was washed with CH_2Cl_2 (10 ml × 2). The aqueous layer was concentrated under reduced pressure and the residue was treated with Dowex 1 × 4 (AcO^- form), which was eluted with 2 N AcOH. The eluate was concentrated under reduced pressure to give 52 mg of the amino acid **8** (98%) as a white solid, which was recrystallized from aqueous EtOH to afford colorless prisms, mp 258 °C (dec.). ^{1}H-NMR (D_2O) δ: 1.70—1.91 (3H, m, 4-H, 3-H), 1.92—2.10 (1H, m, 3-H), 2.73—2.80 (1H, m, 5-H), 3.12 (1H, dd, J=13.2, 4.0 Hz, 6-H), 3.46 (1H, dd, J=13.2, 5.1 Hz, 6-H), 3.65 (1H, dd, J=9.2, 4.4 Hz, 5-H). ^{13}C-NMR (D_2O) δ: 24.22 (t), 24.32 (t), 37.74 (d), 44.12 (t), 58.20 (d), 173.88 (s), 177.69 (s). IR ν_{max}^{KBr} cm^{-1}: 3272 (OH), 1712 (C=O), 1632 (C=O). MS (FAB) *m/z*: 174 (M^++1). *Anal.* Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.53; H, 6.49; N, 8.13.

From **7b**: The ester **7b** was treated similarly to **7a**, giving **8** quantitatively.

From **7c**: Zinc dust (260 mg, 3.98 mmol) was added to a solution of **7c** (160 mg, 0.459 mmol) in AcOH (3 ml) and the mixture was stirred at room temperature for 48 h. It was filtered with suction and the filtrate was concentrated under reduced pressure. The residue was treated with Dowex 1 × 4 (AcO^- form), which was eluted with 2 N AcOH. The eluate was concentrated under reduced pressure to give 49 mg of the amino acid **8** (62%).

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