Stereospecific Synthesis of Cyclic Hydrazoacetic Acids and *meso*-Diaminodicarboxylic Acids

Yasushi ARAKAWA,* Takahiro GOTO, Kazuya KAWASE, and Shigeyuki YOSHIFUJI

Faculty of Pharmaceutical Sciences, Hokuriku University, Kanagawa-machi Ho-3, Kanazawa 920–1181, Japan.
Received October 28, 1997; accepted January 15, 1998

The hetero Diels–Alder adducts 6a—d derived from azodibenzoyl and cyclic dienes were oxidized by ruthenium tetroxide and transformed into *meso*-diaminodicarboxylic acids 12a—d *via* the new cyclic hydrazoacetic acids 9a—d.

Key words *meso*-diaminodicarboxylic acid; hydrazoacetic acid; Diels-Alder adduct; ruthenium tetroxide; azodibenzoyl; *meso*-diaminopimelic acid

Hydrazoacetic acid (**1a**) and its substituted forms (*e.g.* **1b**, **c** and **2**) have been the subject of few reports until now, although many reports on the structurally analogous α-hydrazino acids have been published.[1] This is because of the versatile biological activities (potential antimetabolism, inhibition of amino acid decarboxylase, inhibition of the growth of cell and the transport activity, *etc.*) of the latter. The tetramethyl and dimethyl forms, **1b** and **1c**, were synthesized by Thiele *et al.* in 1896[2] and 1898,[3] respectively. Although 4-phenyl-3,5-pyrazolidinedicarboxylic acid (**2**), one of the cyclic hydrazoacetic acids, was synthesized by Buchner in 1903,[4] a long time had passed until the unsubstituted hydrazoacetic acid was synthesized by Gisin and Brenner in 1970.[5] These methods do not involve any stereochemical considerations and Gisin's method[5] seems to be lengthy.

Meanwhile, diaminodicarboxylic acids, which seem to be formed from cyclic hydrazoacetic acids, play important roles in organic chemistry and biochemistry as "bis"-amino acids. Diaminoglutaric acid complexed with platinum exhibits antitumor activity,[6] while diaminoadipic acid is an inhibitor of bacterial growth,[7] and its *meso*-form is an important source of some medicinal compounds.[8] The usual methods for synthesizing the *meso*-forms start with non-stereocontrolled α,α′-dibromination of α,ω-dicarboxylic acids followed by separation of the resulting stereoisomers.[8] Diaminopimelic acid (DAP) is an important amino acid synthesized by bacteria and higher plants. *meso*-DAP is a biosynthetic precursor of the essential amino acid L-lysine and serves as a cross-linking constituent in virtually all Gram-negative and some Gram-positive bacterial peptidoglycans as well as anchoring various membrane-associated macromolecules, such as lipoproteins, to the cell wall.[9] In spite of the simplicity of its molecular structure, there are few reports of the stereochemical synthesis of *meso*-DAP or its derivatives, except for two recent papers.[9,10] In those reports, Williams and Yuan used optically active diphenyloxazinones[9] and Jurgens used optically active Garner oxazoline.[10] Both methods seem to be expensive and complicated.

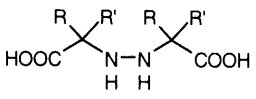
We now wish to report the stereospecific synthesis of the diaminodicarboxylic acids using hetero Diels–Alder adducts *via* the new cyclic hydrazoacetic acids (Chart 1).[11]

First, we planned to synthesize unsubstituted hydrazoacetic acid (**1a**). Azodibenzoyl and butadiene were treated as described in the literature[12a] to give the hetero Diels–Alder adduct **3a**. Its double bond was oxidized under a variety of conditions to investigate the most suitable reaction condition for generating 1,4-dicarboxylic acid, which was then treated with diazomethane and following isolation and purification gave the methyl ester **4a**. For an oxidizing agent, we compared potassium permanganate ($KMnO_4$) with ruthenium tetroxide (RuO_4) (Table 1).

Using $KMnO_4$ in the presence of phase-transfer catalysts, the yields of the desired compound **4a** were lower and the by-product **5** was obtained. However, using RuO_4, chemoselective oxidation of **3a** was accomplished at 0 °C for 12 h; the yield was higher and no formation of compound **5** was detected by TLC although RuO_4 is known to oxidize alcohols, olefins, aromatic rings, and *N*-acylamines.[13] Therefore, RuO_4 is superior to $KMnO_4$.

Compound **4a** was heated in 6 N HCl–AcOH under an argon atmosphere at 100 °C to produce hydrolysis, but unexpectedly, that resulted in the formation of glycine without any desired **1a**. So the *N*-protecting group was changed to *tert*-butoxycarbonyl (Boc) which could be removed under milder acidic conditions. Di-*tert*-butyl azodicarboxylate[14] was treated with butadiene similarly to azodibenzoyl to give Diels–Alder adduct **3b** in 97% yield. Oxidation of the olefin **3b** with RuO_4, followed by treatment with diazomethane, afforded compound **4b** in 88% yield. Compound **4b** was heated in 6 N HCl–AcOH at 70 °C for 8 h to give hydrazoacetic acid in 95% yield as the dihydrochloride, and the free was liberated by treatment with pyridine in MeOH under argon (83% from **4b**).

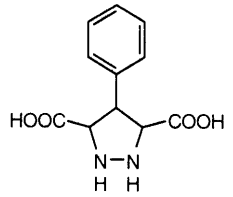
Next, we tried to synthesize the new cyclic hydrazoacetic acids. As di-*tert*-butyl azodicarboxylate is less reactive with most cyclic dienes,[14a] azodibenzoyl was selected as the dienophile and the Diels–Alder adducts **6a—d**



1a: R = H, R′ = H

1b: R = CH_3, R′ = H

1c: R = CH_3, R′ = CH_3



2

Fig. 1

* To whom correspondence should be addressed.

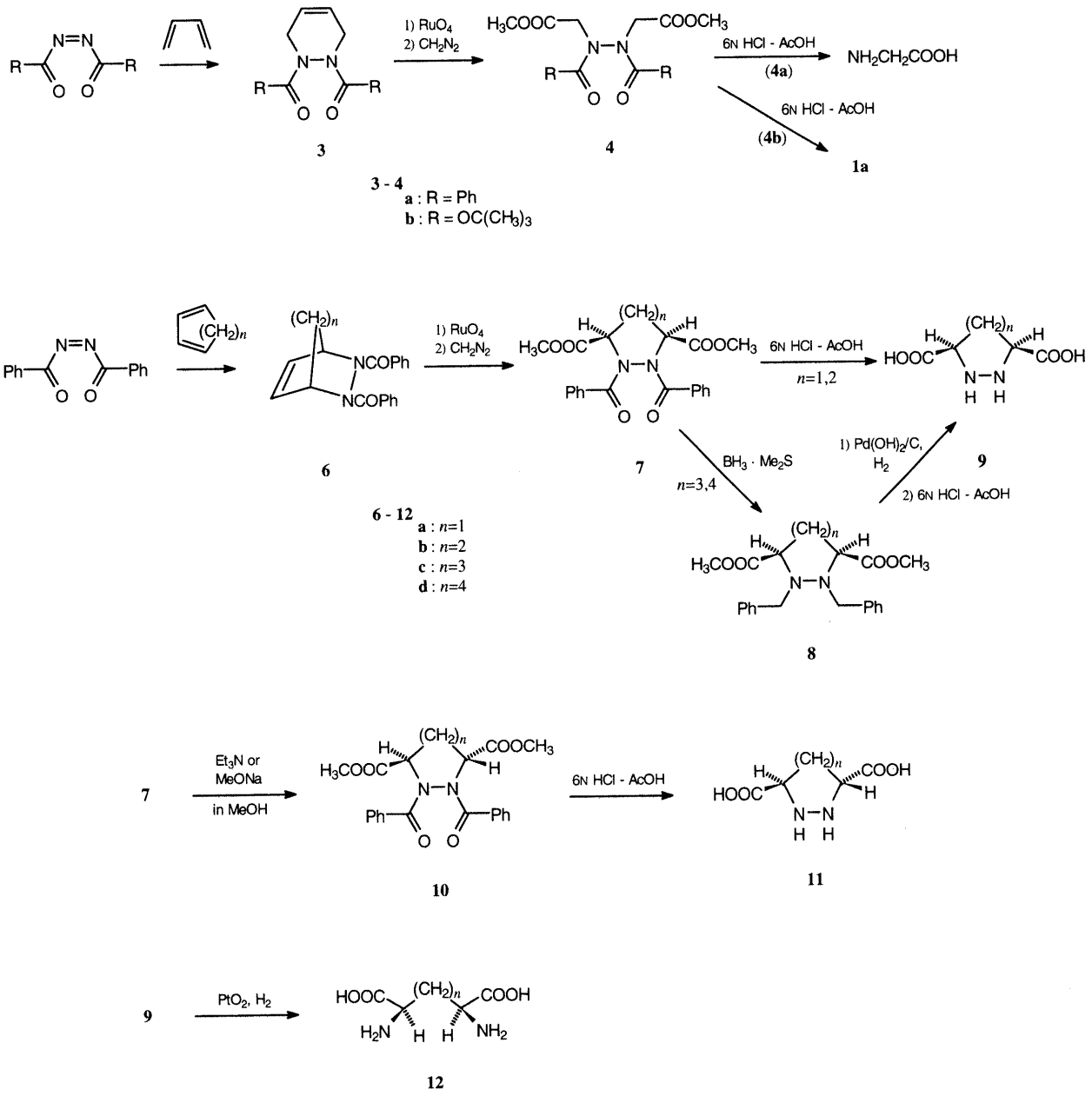
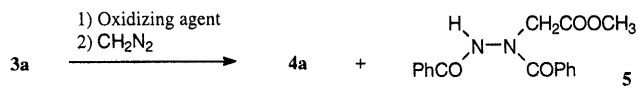


Chart 1

Table 1. Oxidation of Olefin **3a**



Reaction conditions					Yield (%)	
Oxidizing agent	Phase-transfer cat.	Solvent	Temp (°C)	Time (h)	Diester **4a**	Monoester **5**
$KMnO_4$	18-Crown-6 (1/10 mol eq)	Benzene	6	24	—[a]	—
	Dicyclohexano-18-crown-6	Benzene	6	24	—[a]	—
	Bu_4NBr	Benzene H_2O	6	24	55	15
		AcOEt H_2O	0	24	58	14
RuO_4	—	AcOEt 10%$NaIO_4$	0	12	82	—

a) The recovery of **3a** was 40%.

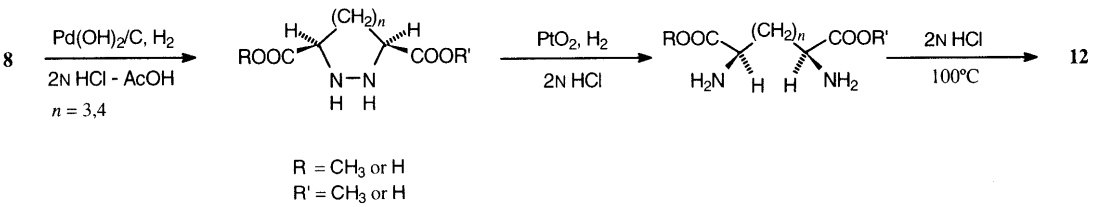


Chart 2

were prepared according to the reported procedures.[12] Oxidation of compounds **6a**—**d** with RuO_4 followed by treatment with diazomethane or thionyl chloride–methanol gave dimethyl esters **7a**—**d** in 89, 95, 93, and 91% yields, respectively. Hydrolysis of compounds **7a** and **7b** in 6 N HCl–AcOH at 100 °C for 24 h gave the desired cyclic hydrazoacetic acids **9a** and **9b** as dihydrochlorides both in 98% yield, unlike the case of **1a**. The free forms of cyclic hydrazoacetic acids **9a** and **9b** could be obtained by adjustment of solutions of their salts to pH 4 under an argon atmosphere. The dimethyl ester **7c** bearing a seven-membered ring was similarly hydrolyzed, but a little epimerization occurred to give a mixture of *cis*- and *trans*-dicarboxylic acids which were difficult to separate. Therefore, an alternative method was attempted, in which the *N*-benzoyl groups of compound **7c** were reduced by borane–dimethyl sulfide in tetrahydrofuran (THF) to give di-*N*-benzyl compound **8c** in 60% yield. This was then debenzylated by hydrogenolysis with 20% $Pd(OH)_2/C$ and hydrolyzed with 2 N HCl at 50 °C for 12 h to give the seven-membered *cis*-hydrazoacetic acid **9c** (1,2-diazepane-*cis*-3,7-dicarboxylic acid) in 88% yield as the dihydrochloride without formation of the epimer. Compound **7d** bearing an eight-membered ring was similarly treated to give the desired eight-membered *cis*-hydrazoacetic acid **9d** (1,2-diazocane-*cis*-3,8-dicarboxylic acid).

Next, in order to obtain the new cyclic *trans*-hydrazoacetic acids, our investigation into the efficient epimerizations of **7a**—**d** was undertaken. In the case of the five-membered dimethyl ester **7a**, when it was treated with triethylamine in methanol under reflux, mono-debenzoylation merely took place without epimerization. When treated with sodium methoxide in methanol, the expected epimerization occurred together with debenzoylation. Treatment of the reaction mixture with dry hydrogen chloride and benzoyl chloride–pyridine, followed by separation on silica gel column chromatography, gave *trans*-diester **10a** in 30% yield with recovery of **7a** (52%). As for the six-membered **7b**, epimerization easily occurred following treatment with triethylamine in methanol under reflux to give *trans*-diester **10b** in 52% yield. When **10b** so obtained was treated similarly to **7b**, **7b** was detected in the reaction mixture by TLC, which indicates an equilibrium between the *cis*- and *trans*-epimers under these reaction conditions. On the other hand, when the seven-membered **7c** was treated similarly to **7b**, debenzoylation mainly took place, even at 40 °C. At room temperature, the desired epimerization occurred without debenzoylation to give *trans*-diester **10c** in 47% yield. Epimerization of the eight-membered **7d** was also examined, but treatment with triethylamine under similar conditions produced no reaction and treatment with sodium methoxide followed by dry hydrogen chloride and benzoyl chloride–pyridine gave neither the desired epimer nor **7d**.

The *trans*-diesters **10a**—**c** were heated in 6 N HCl–AcOH at 100 °C for 24 h to give the corresponding (±)-*trans*-hydrazoacetic acids **11a**—**c** in 40, 49, and 50% yields, respectively. As for the seven-membered **10c**, the hydrolysis mixture contained epimer **9c** (*ca.* 10%), but free **11c** was easily purified because it crystallized readily.

Meanwhile, the *cis*-hydrazoacetic acids **9a**—**d** were converted into the corresponding *meso*-diaminodicarboxylic acids **12a**—**d**. Hydrogenolysis of the N–N bonds of *cis*-hydrazoacetic acids **9a** and **9b** was accomplished with PtO_2 in 2 N HCl at atmospheric pressure to give *meso*-2,4-diaminoglutaric acid (**12a**) and *meso*-2,5-diaminoadipic acid (**12b**) in 99 and 100% (dihydrochlorides) yields, respectively. On the other hand, hydrogenolysis of **9c** and **9d** needed to be conducted at 4 atm to give *meso*-2,6-diaminopimelic acid (**12c**, *meso*-DAP) and *meso*-2,7-diaminosuberic acid (**12d**) in 92 and 93% (dihydrochlorides) yields, respectively. We discovered more convenient synthetic routes from **8c** to **12c** and from **8d** to **12d** (Chart 2), which involve the change of the sequence of the reactions to debenzylation, reduction of the N–N bond, and hydrolysis. There is less risk of epimerizations or side-reactions as the hydrolysis stages were after the N–N scissions, and the yields rose to 97 and 97% (from **8c** and **8d**, dihydrochlorides), respectively.

In conclusion, we have developed a stereospecific synthesis for the new cyclic hydrazoacetic acids and the *meso*-diaminodicarboxylic 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 amino acids on a GSX-400 spectrometer with tetramethylsilane as an internal standard. For amino acids, analyses were performed in 1 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). 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) or alumina (Aluminium oxide 90, 70—230 mesh, Merck). Flash chromatography was performed on silica gel (Silica Gel 60, 230—400 mesh, Nacalai Tesque).

1,2-Dibenzoyl-1,2,3,6-tetrahydropyridazine (3a) Under conditions preventing light-transmittance, azodibenzoyl 1.00 g (4.20 mmol), was dissolved in CH_2Cl_2 (50 ml) and the solution was cooled to −50 °C. Excess 1,3-butadiene gas was passed into the solution and the reaction vessel was made airtight. The mixture was stirred at room temperature for 14 h. The reaction solution was then concentrated under reduced pressure and the residue was recrystallized from EtOH to give compound **1a** (1.03 g, 84%) as colorless prisms, mp 163—164.5 °C (lit.,[12a] mp 163—164 °C). ^{1}H-NMR[15] ($CDCl_3$) δ: 3.95—4.20 (3H, m, 3-H and 6-Ha),

4.70—4.95 (1H, m, 6-Hb), 5.65—6.05 (2H, m, –HC=CH–), 6.98—7.88 (10H, m, aromatic H). ^{13}C-NMR[15] ($CDCl_3$) δ: 41.65 (t), 49.25 (t), 122.59 (d), 124.33 (d), 126.70 (d), 127.08 (d), 128.31 (d), 128.42 (d), 130.43 (d), 131.18 (d), 133.42 (s), 134.85 (s), 171.30 (s), 171.34 (s). IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O), 1650 (C=O). MS *m/z*: 292 (M^+). *Anal.* Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 73.73; H, 5.46; N, 9.45.

Dimethyl 3,4-Dibenzoyl-3,4-diazahexanedioate (4a) A solution of **3a** (1.00 g, 3.42 mmol) in AcOEt (100 ml), $RuO_2 \cdot xH_2O$ (10 mg) and a 10% $NaIO_4$ solution (35 ml) were mixed and then vigorously stirred at 0 °C for 12 h. The AcOEt layer was separated and the aqueous layer was extracted with AcOEt (50 ml × 4). Isopropyl alcohol (3 ml) was added to the combined AcOEt layers 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 residue was dissolved in MeOH (10 ml) and treated with diazomethane. The solution was concentrated and the residual black oil was subjected to column chromatography on silica gel (CH_2Cl_2) to give a colorless oil, which was recrystallized from diisopropyl ether–$CHCl_3$, giving **4a** (1.08 g, 82%) as colorless prisms, mp 120—121 °C. ^{1}H-NMR[15] ($CDCl_3$) δ: 3.55—3.75 (6H, m, 2 × CH_3), 4.07—5.18 (4H, m, 2 × CH_2), 6.92—7.59 (10H, m, aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 50.27 (t), 52.29 (q), 52.50 (q), 55.62 (t), 126.12 (d), 126.35 (d), 128.45 (d), 128.64 (d), 130.46 (d), 130.62 (d), 133.62 (s), 134.74 (s), 169.73 (s), 170.37 (s), 170.93 (s), 172.36 (s). IR ν_{max}^{KBr} cm^{-1}: 1754 (C=O), 1684 (C=O). MS *m/z*: 384 (M^+). *Anal.* Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.49; H, 5.21; N, 7.19.

Oxidation of 3a with Potassium Permanganate A solution of **3a** (1.00 g, 3.42 mmol) in AcOEt (50 ml) was added dropwise to a mixture of potassium permanganate (1.70 g, 10.8 mmol), tetrabutylammonium bromide (3.44 g, 10.7 mmol), AcOEt (20 ml) and water (30 ml) at 0 °C with vigorous stirring and then stirred at 0 °C for 24 h. Isopropyl alcohol (6 ml) was added and the mixture was stirred at room temperature for 2 h. The precipitate was filtered off with the aid of a Hyflo Super-Cel (Johns-Manville) and a 10% HCl was added to the filtrate until the pH of the aqueous layer reached 2. The AcOEt layer was separated and the aqueous layer was extracted with AcOEt (50 ml × 3). The combined AcOEt layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in MeOH and treated with diazomethane. The solution was concentrated and the residue was subjected to column chromatography on silica gel ($CHCl_3$: hexane : AcOEt = 25 : 25 : 2), giving **4a** (765 mg, 58%) and methyl 3,4-dibenzoyl-3,4-diazabutanoate (**5**, 150 mg, 14%) which was recrystallized from $CHCl_3$–diisopropyl ether to afford colorless prisms, mp 112—113 °C. The analytical data of **5** were as follows. ^{1}H-NMR ($CDCl_3$) δ: 3.71 (3H, s, CH_3), 4.64 (2H, br s, CH_2), 7.27—7.60 (10H, m, aromatic H), 8.78 (1H, s, NH). ^{13}C-NMR ($CDCl_3$) δ: 49.01 (t), 52.44 (q), 127.28 (d), 127.38 (d), 128.13 (d), 128.76 (d), 130.86 (d), 131.59 (s), 132.59 (d), 133.58 (s), 166.26 (s), 170.23 (s), 172.97 (s). IR ν_{max}^{KBr} cm^{-1}: 3164 (NH), 1758 (C=O), 1668 (C=O). MS *m/z*: 312 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.24; H, 5.22; N, 8.86.

Di-*tert*-butyl 1,2,3,6-Tetrahydropyridazine-1,2-dicarboxylate (3b) 1,3-Butadiene gas was passed into a solution of di-*tert*-butyl azodicarboxylate (5.00 g, 21.7 mmol) in CCl_4 (50 ml) at −40 °C until the volume increased by 20 ml. The reaction vessel was made airtight, and the mixture was stirred at room temperature for 1 week. The reaction mixture was then concentrated under reduced pressure and the residue was subjected to column chromatography on silica gel (hexane : AcOEt = 3 : 1) to give **3b** (6.00 g, 97%) as a white solid, mp 73—74 °C (lit.,[14b] mp 73—74.5 °C).

Dimethyl 3,4-Di-*tert*-butoxycarbonyl-3,4-diazahexanedioate (4b) A solution of **3b** (3.00 g, 10.6 mmol) in AcOEt (50 ml), $RuO_2 \cdot xH_2O$ (30 mg) and a 10% $NaIO_4$ solution (100 ml) were mixed and then 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 layers and the solution was left to stand for 1 h. The precipitated RuO_2 was filtered off and the solution was dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was dissolved in MeOH (10 ml) and treated with diazomethane. The solution was concentrated and the residual black oil was subjected to column chromatography on alumina ($CHCl_3$) to give **4b** (3.50 g, 88%) as a colorless oil. ^{1}H-NMR[15] ($CDCl_3$) δ: 1.30—1.50 (18H, m, 2 × $C(CH_3)_3$), 3.70 (6H, m, 2 × OCH_3), 3.85—4.15 and 4.35—4.80 (4H, m, 2 × CH_2). ^{13}C-NMR[15] ($CDCl_3$) δ: 28.07 (q), 28.13 (q), 28.20 (q), 51.46 (t), 51.93 (t), 52.02 (q), 52.10 (q), 52.90 (q), 53.66 (t), 81.88 (s), 82.00 (s), 82.29 (s), 82.36 (s), 153.48 (s), 153.66 (s), 154.07 (s), 154.54 (s), 170.14 (s), 170.57 (s), 170.70 (s). IR ν_{max}^{neat} cm^{-1}: 1758 (C=O), 1726 (C=O). MS *m/z*: 376 (M^+).

Hydrazoacetic Acid (1a) Compound **4b** (1.00 g, 2.66 mmol) was heated in AcOH (20 ml) and 6 N HCl (20 ml) at 70 °C for 8 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give hydrazoacetic acid dihydrochloride (560 mg, 95%) as a pale yellow oil. It was then dissolved in MeOH (20 ml) and pyridine (4 ml) was added to the solution, giving free **1a** (325 mg, 83%) as colorless prisms, mp 142—144 °C (dec.) (lit.,[5] mp 147—149 °C). ^{1}H-NMR (1 N DCl) δ: 4.01 (s). ^{13}C-NMR (1 N DCl) δ: 50.17 (t), 171.26 (s). IR ν_{max}^{KBr} cm^{-1}: 3304, 2736, 1720 (C=O), 1612 (C=O). MS (FAB) *m/z*: 149 ($M^+ + 1$). *Anal.* Calcd for $C_4H_8N_2O_4$: C, 32.44; H, 5.44; N, 18.91. Found: C, 32.42; H, 5.44; N, 18.78.

2,3-Dibenzoyl-2,3-diazabicyclo[2.2.1]hept-5-ene (6a) Under conditions preventing light-transmittance, azodibenzoyl (0.30 g, 1.26 mmol) was dissolved in $CHCl_3$ (10 ml) and the solution was cooled to −50 °C. Cyclopentadiene (2 ml) obtained from pyrolysis of dicyclopentadiene was added to the solution and the mixture was stirred at room temperature. The reaction mixture became colorless after 5—10 min. The reaction solution was concentrated under reduced pressure and the residue was recrystallized from EtOH to give compound **6a** (0.38 g, 99%) as colorless prisms, mp 138—139 °C (lit.,[12c] mp 138—139 °C).

2,3-Dibenzoyl-2,3-diazabicyclo[2.2.2]oct-5-ene (6b) Under conditions preventing light-transmittance, 1,3-cyclohexadiene (1.20 g, 15 mmol) was added to a solution of azodibenzoyl (1.19 g, 5.0 mmol) in CCl_4 (20 ml) and the solution was stirred at room temperature for 20 h. The reaction solution was concentrated under reduced pressure and the residue was recrystallized from EtOH to give compound **6b** (0.96 g, 60%) as colorless prisms, mp 157—158 °C (lit.,[12c] mp 157—158 °C).

6,7-Dibenzoyl-6,7-diazabicyclo[3.2.2]non-8-ene (6c) Under conditions preventing light-transmittance, 1,3-cycloheptadiene (0.82 g, 8.5 mmol) was added to a solution of azodibenzoyl (1.00 g, 4.2 mmol) in CCl_4 (25 ml) and the solution was refluxed for 16 h. The reaction solution was concentrated under reduced pressure and the residue was triturated in cold benzene. After filtration, the resultant white solid was recrystallized from EtOH to give compound **6c** (1.30 g, 93%) as colorless prisms, mp 202—203 °C (lit.,[12c] mp 203—204 °C).

7,8-Dibenzoyl-7,8-diazabicyclo[4.2.2]dec-9-ene (6d) Under conditions preventing light-transmittance, a mixture of 1,3-cyclooctadiene (20 ml) and azodibenzoyl (10.0 g, 42.0 mmol) was heated at 100 °C for 16 h. After cooling, the reaction mixture was triturated in cold hexane and filtered. The resultant white solid was recrystallized from EtOH to give compound **6d** (5.38 g, 37%) as colorless prisms, mp 209.5—211.5 °C (lit.,[12c] mp 207—208 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.60—2.68 (8H, m, 4 × CH_2), 4.44 (1H, dd, J = 9.9, 4.0 Hz, 1-H), 5.30 (1H, dd, J = 6.9, 4.8 Hz, 6-H), 5.98 (1H, dd, J = 9.9, 5.4 Hz, 6-H), 6.02 (1H, dd, J = 9.9, 6.2 Hz, 6-H), 7.16—7.71 (10H, m, aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 22.81 (t), 25.43 (t), 31.04 (t), 31.75 (t), 52.91 (d), 57.53 (d), 127.37 (d), 127.49 (d), 128.57 (d), 129.31 (d), 129.59 (d), 129.96 (d), 131.26 (d), 134.09 (s), 135.36 (s), 169.25 (s), 174.49 (s). IR ν_{max}^{KBr} cm^{-1}: 1684 (C=O), 1642 (C=O). MS *m/z*: 346 (M^+). *Anal.* Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.52; H, 6.36; N, 7.94.

Dimethyl 1,2-Dibenzoylpyrazolidine-*cis*-3,5-dicarboxylate (7a) A solution of **6a** (1.00 g, 3.29 mmol) in AcOEt (30 ml), $RuO_2 \cdot xH_2O$ (10 mg) and a 10% $NaIO_4$ solution (35 ml) were mixed and then vigorously stirred at 0 °C for 7 h. The AcOEt layer was separated and the aqueous layer was extracted with AcOEt (50 ml × 6). Isopropyl alcohol (3 ml) was added to the combined AcOEt layers 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 residue was dissolved in MeOH (10 ml) and treated with diazomethane. The solution was concentrated and the residual black oil was subjected to column chromatography on silica gel (hexane : AcOEt = 3 : 1) to give a white solid, which was recrystallized from $CHCl_3$–hexane, giving **7a** (1.16 g, 89%) as colorless prisms, mp 149—150 °C. ^{1}H-NMR[15] ($CDCl_3$) δ: 2.36—2.87 (2H, m, CH_2), 3.40—4.15 (6H, m, 2 × CH_3), 4.77 (2H, d, J = 8.4 Hz, 3- and 5-H), 7.27—7.47 (6H, m, aromatic H), 7.69—8.12 (4H, m, aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 33.35 (t), 52.49 (q), 53.52 (q), 56.88 (d), 63.40 (d), 128.56 (d), 128.83 (d), 130.90 (d), 131.60 (s), 132.80 (d), 133.91 (s), 167.90 (s), 169.20 (s), 170.04 (s), 172.59 (s). IR ν_{max}^{KBr} cm^{-1}: 1758 (C=O), 1694 (C=O). MS *m/z*: 396 (M^+). *Anal.* Calcd for $C_{21}H_{20}N_2O_6$: C, 63.63; H, 5.09; N, 7.07. Found: C, 63.86; H, 5.09; N,

6.93. Dimethyl 1-benzoylpyrazolidine-*cis*-3,5-dicarboxylate was also obtained in 3% yield (30 mg, 0.10 mmol) from the earlier fraction of the chromatography for **7a** as a white solid, which was recrystallized from $CHCl_3$–hexane, giving colorless prisms, mp 129—130 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.94—2.38 (1H, m, 4-Ha), 2.71—3.04 (1H, m, 4-Hb), 3.76 (3H, s, CH_3), 3.78 (3H, s, CH_3), 3.40—4.10 (1H, m, NH), 5.00—5.22 (2H, m, 3- and 5-H), 7.27—7.50 (3H, m, aromatic H), 7.74—7.90 (2H, m, aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 36.40 (t), 52.66 (q), 58.27 (d), 60.39 (d), 127.72 (d), 129.19 (d), 130.95 (d), 133.93 (s), 169.67 (s), 170.48 (s), 171.58 (s). IR ν_{max}^{KBr} cm^{-1}: 3216 (NH), 1742 (CO), 1632 (C=O). MS *m/z*: 292 (M^+). *Anal.* Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.32; H, 5.44; N, 9.49.

Dimethyl 1,2-Dibenzoylperhydropyridazine-*cis*-3,6-dicarboxylate (7b) A solution of **6b** (1.00 g, 3.14 mmol) in AcOEt (30 ml), $RuO_2 \cdot xH_2O$ (10 mg) and a 10% $NaIO_4$ solution (35 ml) were mixed and then vigorously stirred at 0 °C for 6 h. The AcOEt layer was separated and the aqueous layer was extracted with AcOEt (50 ml × 4). Isopropyl alcohol (3 ml) was added to the combined AcOEt layers 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 residue was dissolved in MeOH (10 ml) and treated with diazomethane. The solution was concentrated and the residual black oil was subjected to column chromatography on silica gel ($CHCl_3$) to give a colorless oil, which was recrystallized from benzene–hexane, giving **7b** (1.23 g, 95%) as colorless prisms, mp 138—139 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.89 (2H, m, 4- and 5-H), 2.14—2.17 (1H, m, 4-H), 2.26—2.30 (1H, m, 5-H), 3.73 (3H, s, CH_3), 3.79 (3H, s, CH_3), 4.55 (1H, m, 3-H), 4.66 (1H, s, 6-H), 7.29—7.75 (10H, m, aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 22.14 (t), 22.36 (t), 52.37 (q), 52.66 (q), 56.99 (d), 60.48 (d), 127.43 (d), 127.64 (d), 127.81 (d), 127.87 (d), 128.00 (d), 128.88 (d), 130.50 (d), 132.04 (d), 132.52 (s), 134.10 (s), 169.44 (s), 170.28 (s), 173.07 (s), 174.15 (s). IR ν_{max}^{KBr} cm^{-1}: 1754 (C=O), 1690 (C=O). MS *m/z*: 410 (M^+). *Anal.* Calcd for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.44; H, 5.40; N, 6.80.

Dimethyl 1,2-Dibenzoyl-1,2-diazepane-*cis*-3,7-dicarboxylate (7c) A solution of **6c** (1.00 g, 3.01 mmol) in AcOEt (200 ml), $RuO_2 \cdot xH_2O$ (10 mg) and a 10% $NaIO_4$ solution (35 ml) were mixed and then vigorously stirred at 0 °C for 8 h. The AcOEt layer was separated and the aqueous layer was extracted with AcOEt (50 ml × 6). Isopropyl alcohol (3 ml) was added to the combined AcOEt layers 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 residue was dissolved in MeOH (10 ml) and treated with diazomethane. The solution was concentrated and the residual black oil was subjected to column chromatography on silica gel ($CHCl_3$) to give a colorless oil, which was recrystallized from AcOEt–hexane, giving **7c** (1.19 g, 93%) as colorless prisms, mp 124—125 °C. ^{1}H-NMR[15] ($CDCl_3$) δ: 1.69—2.43 (6H, m, 3 × CH_2), 3.46 (3H, br s, CH_3), 3.76 (3H, br s, CH_3), 4.59—4.80 (2H, m, 3- and 7-H), 7.23—7.58 (10H, m, aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 21.80 (t), 25.76 (t), 27.20 (t), 52.26 (q), 62.71 (d), 63.65 (d), 126.96 (d), 127.34 (d), 127.63 (d), 128.63 (d), 130.10 (d), 130.98 (d), 133.80 (s), 135.19 (s), 168.91 (s), 170.07 (s), 173.42 (s). IR ν_{max}^{KBr} cm^{-1}: 1754 (C=O), 1678 (C=O). MS *m/z*: 424 (M^+). *Anal.* Calcd for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 65.17; H, 5.66; N, 6.62.

Dimethyl 1,2-Dibenzoyldiazocane-*cis*-3,8-dicarboxylate (7d) A solution of **6d** (1.00 g, 2.89 mmol) in AcOEt (240 ml), $RuO_2 \cdot xH_2O$ (10 mg) and a 10% $NaIO_4$ solution (35 ml) were mixed and then vigorously stirred at 0 °C for 12 h. The AcOEt layer was separated and the aqueous layer was extracted with AcOEt (50 ml × 6). Isopropyl alcohol (3 ml) was added to the combined AcOEt layers 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 residue was dissolved in MeOH (10 ml) and treated with diazomethane. The solution was concentrated and the residue was subjected to column chromatography on silica gel ($CHCl_3$) to give a colorless oil, which was recrystallized from AcOEt, giving **7d** (1.15 g, 91%) as colorless prisms, mp 218—220 °C. ^{1}H-NMR[15] ($CDCl_3$) δ: 0.96—2.59 (8H, m, 4 × CH_2), 2.70—4.10 (6H, m, 2 × CH_3), 4.22—4.38 (1H, m, 3-H), 4.85—5.54 (1H, m, 8-H), 7.12—7.57 (10H, m, aromatic H). ^{13}C-NMR[15] ($CDCl_3$) δ: 24.07 (t), 25.67 (t), 26.00 (t), 28.30 (br t), 29.30 (t), 51.99 (q), 52.25 (q), 58.36 (d), 63.07 (d), 65.01 (d), 125.39 (d), 127.00 (d), 127.09 (d), 127.26 (d), 127.91 (d), 127.99 (d), 128.57 (d), 128.73 (d), 129.38 (d), 129.93 (d), 130.10 (s), 130.37 (d), 134.27 (s), 134.58 (s), 135.08 (s), 136.31 (s), 168.58 (br s), 169.79 (s), 170.60 (s), 171.73 (s), 174.04 (s). IR ν_{max}^{KBr} cm^{-1}: 1766 (C=O), 1750 (C=O), 1672 (C=O). MS *m/z*: 438 (M^+). *Anal.* Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.01; H, 6.07; N, 6.34.

Dimethyl 1,2-Dibenzyl-1,2-diazepane-*cis*-3,7-dicarboxylate (8c) A solution of **7c** (424 mg, 1.00 mmol) in THF (15 ml) was added dropwise to a mixture of borane–dimethyl sulfide complex (1 ml) and THF (5 ml) at 0 °C with stirring under an argon atmosphere, and the mixture was left to stand at 5 °C for 24 h. Tetramethylethylenediamine (0.8 ml) was added to the reaction mixture at 0 °C and the mixture was stirred for 30 min. The white precipitate was filtered off and the filtrate was concentrated under reduced pressure. Et_2O (20 ml) was added to the residue and the precipitate was filtered off. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography on silica gel (hexane : Et_2O = 3 : 1) to give **8c** (238 mg, 60%) as a colorless oil. ^{1}H-NMR[15] ($CDCl_3$) δ: 1.48—2.30 (6H, m, 3 × CH_2), 3.45 (6H, s, 2 × CH_3), 3.60—4.80 (2H, m, 3- and 7-H), 3.88—4.20 (4H, m, 2 × Bn-H_2), 7.05—7.30 (10H, m, aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 25.61 (t), 27.55 (t), 29.20 (t), 51.52 (q), 58.55 (t), 59.05 (t), 63.46 (d), 69.82 (d), 126.56 (d), 126.93 (d), 127.61 (d), 127.84 (d), 129.43 (d), 138.33 (s), 139.34 (s), 172.95 (s), 173.98 (s). IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O). MS *m/z*: 396 (M^+).

Dimethyl 1,2-Dibenzyl-1,2-diazocane-*cis*-3,8-dicarboxylate (8d) A solution of **7d** (438 mg, 1.00 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a mixture of borane–dimethyl sulfide complex (1 ml) and THF (10 ml) at 0 °C with stirring under an argon atmosphere, and the mixture was left to stand at 5 °C for 24 h. Tetramethylethylenediamine (0.8 ml) was added to the reaction mixture at 0 °C and the mixture was stirred for 30 min. The white precipitate was filtered off and the filtrate was concentrated under reduced pressure. Et_2O (20 ml) was added to the residue and the precipitate was filtered off. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography on silica gel (hexane : Et_2O = 3 : 1) to give a white solid, which was recrystallized from hexane, giving **8d** (226 mg, 55%) as colorless prisms, mp 102—103.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.82—0.93 (1H, m, 6-Ha), 1.54—1.88 (5H, m, 4-Ha, 5-Ha, Hb, 6-Hb, and 7-Ha), 2.29—2.49 (2H, m, 4-Hb and 7-Hb), 2.99 (3H, s, CH_3), 3.03 (1H, dd, J = 11.5, 4.2 Hz, 8-H), 3.58 (3H, s, CH_3), 3.60 (1H, d, J = 14.3 Hz, Bn-Ha), 3.71 (1H, dd, J = 5.9, 1.7 Hz, 3-H), 4.14 (1H, d, J = 11.9 Hz, Bn′-Ha), 4.24 (1H, d, J = 11.9 Hz, Bn′-Hb), 4.63 (1H, d, J = 14.3 Hz, Bn-Hb), 7.15—7.43 (10H, m, aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 24.65 (t, 5-C), 27.47 (t, 6-C), 29.28 (t, 7-C), 32.03 (t, 4-C), 50.32 (t, Bn′-C), 50.84 (q, CH_3), 50.97 (q, CH_3), 57.95 (t, Bn-C), 61.61 (d, 8-C), 67.14 (d, 3-C), 126.81 (d), 127.40 (d), 127.64 (d), 128.42 (s), 129.57 (d), 130.33 (d), 137.80 (s), 139.06 (s), 173.19 (s), 174.13 (s). IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O). MS *m/z*: 410 (M^+). *Anal.* Calcd for $C_{24}H_{30}N_2O_4$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.50; H, 7.47; N, 6.76.

***cis*-3,5-Pyrazolidinedicarboxylic Acid (9a)** Under an argon atmosphere, compound **7a** (2.00 g, 5.05 mmol) was heated in AcOH (100 ml) and 6 N HCl (100 ml) at 100 °C for 24 h. After cooling, AcOH was removed from the reaction mixture under reduced pressure and the residual solution was washed with Et_2O (100 ml × 4) to remove the generated benzoic acid. The aqueous layer was concentrated under reduced pressure to give 1.15 g of the five-membered cyclic hydrazoacetic acid dihydrochloride (98%) as a pale yellow solid. Under an argon atmosphere, the obtained dihydrochloride salt was dissolved in a little water and the pH of the solution was adjusted to 4 with NH_4OH to give free **9a** (404 mg, 50%) as colorless prisms, mp 155—156 °C (dec.). ^{1}H-NMR (1 N DCl) δ: 2.69 (1H, ddd, J = 13.6, 5.5, 5.5 Hz, 4-Ha), 2.96 (1H, ddd, J = 13.6, 9.2, 9.2 Hz, 4-Hb), 4.56 (2H, dd, J = 9.2, 5.5 Hz, 3- and 5-H). ^{13}C-NMR (1 N DCl) δ: 33.49 (t, 4-C), 60.74 (d, 3-C), 60.92 (d, 5-C), 172.20 (s, C=O). IR ν_{max}^{KBr} cm^{-1}: 3260, 3032, 1738 (C=O), 1590 (C=O). MS *m/z*: 160 (M^+). *Anal.* Calcd for $C_5H_8N_2O_4$: C, 37.50; H, 5.04; N, 17.49. Found: C, 37.38; H, 5.01; N, 17.38.

Perhydropyridazine-*cis*-3,6-dicarboxylic Acid (9b) Under an argon atmosphere, compound **7b** (2.00 g, 4.87 mmol) was heated in AcOH (100 ml) and 6 N HCl (100 ml) at 100 °C for 24 h. After cooling, AcOH was removed from the reaction mixture under reduced pressure and the residual solution was washed with Et_2O (100 ml × 4) to remove the generated benzoic acid. The aqueous layer was concentrated under reduced pressure to give 1.18 g of the six-membered cyclic hydrazoacetic acid dihydrochloride (98%) as a pale yellow solid. Under an argon atmosphere, the obtained dihydrochloride salt was dissolved in a little water and the pH of the solution was adjusted to 4 with NH_4OH to

give free **9b** (500 mg, 59%) as colorless prisms, mp 155—156 °C (dec.). ^{1}H-NMR (1 N DCl) δ: 2.01—2.07 (2H, m, 4-Ha and 5-Ha), 2.16—2.22 (2H, m, 4-Hb and 5-Hb), 4.20 (2H, dd, J=6.2, 4.0 Hz, 3- and 6-H). ^{13}C-NMR (1 N DCl) δ: 22.77 (t, 4- and 5-C), 56.04 (d, 3- and 6-C), 172.20 (s, C=O). IR ν_{max}^{KBr} cm^{-1}: 3244, 3096, 1740 (C=O), 1610 (C=O). MS m/z: 174 (M^+). *Anal.* Calcd for $C_6H_{10}N_2O_4$: C, 41.38; H, 5.79; N, 16.09. Found: C, 41.38; H, 5.88; N, 16.15.

1,2-Diazepane-*cis*-3,7-dicarboxylic Acid (9c) Compound **8c** (98 mg, 0.25 mmol) was hydrogenated for debenzylation in AcOH (3 ml) and 2 N HCl (3 ml) in the presence of 20% $Pd(OH)_2$/C (15 mg) under a pressure of 4 atm for 18 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in 2 N HCl (3 ml) and the solution was heated at 50 °C for 12 h. The solution was concentrated under reduced pressure to give 57 mg of the seven-membered cyclic hydrazoacetic acid dihydrochloride (88%) as a pale yellow solid. Under an argon atmosphere, the obtained dihydrochloride salt was dissolved in a little water and the pH of the solution was adjusted to 4 with NH_4OH to give free **9c** (28 mg, 60%) as colorless prisms, mp 192 °C (dec.). ^{1}H-NMR (1 N DCl) δ: 1.76—2.01 (2H, m, 5-H), 2.38—2.45 (4H, m, 4- and 6-H), 4.14 (2H, dd, J=10.4, 5.7 Hz, 3- and 7-H). ^{13}C-NMR (1 N DCl) δ: 22.53 (t, 5-C), 29.80 (t, 4- and 6-C), 62.32 (d, 3- and 7-C), 173.65 (s, C=O). IR ν_{max}^{KBr} cm^{-1}: 3012, 1714 (C=O). MS (FAB) m/z: 189 (M^++1). *Anal.* Calcd for $C_7H_{12}N_2O_4$: C, 44.68; H, 6.43; N, 14.89. Found: C, 44.35; H, 6.29; N, 14.70.

1,2-Diazocane-*cis*-3,8-dicarboxylic Acid (9d) Compound **8d** (101 mg, 0.25 mmol) was hydrogenated for debenzylation in AcOH (3 ml) and 2 N HCl (3 ml) in the presence of 20% $Pd(OH)_2$/C (15 mg) under a pressure of 4 atm for 24 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in 2 N HCl (3 ml) and the solution was heated at 40 °C for 24 h. The solution was concentrated under reduced pressure to give 64 mg of the eight-membered cyclic hydrazoacetic acid dihydrochloride (93%) as a pale yellow solid. Under an argon atmosphere, the obtained dihydrochloride salt was dissolved in a little water and the pH of the solution was adjusted to 4 with NH_4OH to give free **9d** (32 mg, 64%) as colorless prisms, mp 188 °C (dec.). ^{1}H-NMR (1 N DCl) δ: 1.63—1.85 (4H, m, 5- and 6-H), 1.87—2.06 (2H, m, 4-Ha and 7-Ha), 2.11—2.30 (2H, m, 4-Hb and 7-Hb), 4.06 (2H, dd, J=9.5, 3.7 Hz, 3- and 8-H). ^{13}C-NMR (1 N DCl) δ: 24.17 (t, 5- and 6-C), 26.34 (t, 4- and 7-C), 61.56 (d, 3- and 8-C), 173.93 (s, C=O). IR ν_{max}^{KBr} cm^{-1}: 3462, 3312, 1714 (C=O). MS (FAB) m/z: 203 (M^++1). *Anal.* Calcd for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.51; H, 6.91; N, 13.81.

Dimethyl 1,2-Dibenzoylpyrazolidine-*trans*-3,5-dicarboxylate (10a) Under an argon atmosphere, sodium (1.0 g) was added in several portions to MeOH (100 ml) and *cis*-diester **7a** (1.00 g, 2.52 mmol) was then added to the solution. The mixture was refluxed for 24 h. Hydrogen chloride was passed into the solution at 0 °C until it became acidic, then it was concentrated under reduced pressure. Under an argon atmosphere, the residue was mixed with pyridine (10 ml) and benzoyl chloride (2 ml) was added to the mixture at 0 °C, followed by stirring at room temperature for 6 h. Water (50 ml) was added and the mixture was extracted with $CHCl_3$ (50 ml × 6). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and treated with a solution of diazomethane in Et_2O. After evaporation of the solvent, the residue was subjected to flash chromatography on silica gel (hexane : $CHCl_3$: Et_2O = 2 : 1 : 1) to give *trans*-diester **10a** (300 mg, 30%) as a white solid followed by recovery of **7a** (520 mg, 52%). Recrystallization of the obtained **10a** from AcOEt–hexane gave colorless needles, mp 137—138 °C. ^{1}H-NMR[15] ($CDCl_3$) δ: 2.69 (2H, t, J=6.4 Hz, CH_2), 3.75—3.78 (6H, m, 2 × CH_3), 5.04 (2H, br s, 3-H and 5-H), 7.26—7.64 (10H, m, aromatic H). ^{13}C-NMR[15] ($CDCl_3$) δ: 32.68 (t), 52.99 (q), 59.8 (br d), 128.04 (d), 128.22 (d), 131.56 (d), 133.38 (s), 170.28 (s), 172.33 (s). IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O), 1688 (C=O), 1660 (C=O). MS m/z: 396 (M^+). *Anal.* Calcd for $C_{21}H_{20}N_2O_6$: C, 63.63; H, 5.09; N, 7.07. Found: C, 63.78; H, 5.09; N, 7.14.

Dimethyl 1,2-Dibenzoylperhydropyridazine-*trans*-3,6-dicarboxylate (10b) A mixture of *cis*-diester **7b** (1.00 g, 2.44 mmol) and Et_3N (10 ml) in MeOH (50 ml) was refluxed for 24 h. The mixture was concentrated under reduced pressure and the residue was subjected to flash chromatography on silica gel (hexane : AcOEt = 3 : 1) to give *trans*-diester **10b** (522 mg, 52%) as a white solid followed by recovery of **7b** (394 mg, 39%). Recrystallization of the obtained **10b** from AcOEt–hexane gave colorless needles, mp 166—168 °C. ^{1}H-NMR[15] ($CDCl_3$) δ: 1.70—2.35 (4H, m, 2 × CH_2), 3.30—4.00 (6H, m, 2 × CH_3), 4.20—5.75 (2H, m, 3-H and 6-H), 7.20—7.65 (10H, m, aromatic H). ^{13}C-NMR[15] ($CDCl_3$) δ: 20.92 (t), 52 (br d), 52.41 (q), 58 (br d), 127.47 (d), 128.22 (d), 130.97 (d), 134.02 (s), 169.89 (s), 172.45 (s). IR ν_{max}^{KBr} cm^{-1}: 1742 (C=O), 1684 (C=O), 1664 (C=O). MS m/z: 410 (M^+). *Anal.* Calcd for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.38; H, 5.41; N, 6.75.

Dimethyl 1,2-Dibenzoyl-1,2-diazepane-*trans*-3,7-dicarboxylate (10c) A mixture of *cis*-diester **7c** (100 mg, 0.24 mmol) and Et_3N (5 ml) in MeOH (8 ml) was stirred at room temperature for 3 d. The mixture was concentrated under reduced pressure and the residue was subjected to column chromatography on silica gel (hexane : $CHCl_3$: Et_2O = 9 : 4 : 1) to give *trans*-diester **10c** (47 mg, 47%) as a white solid followed by recovery of **7c** (36 mg, 36%). Recrystallization of the obtained **10c** from AcOEt–hexane gave colorless needles, mp 149—150 °C. ^{1}H-NMR[15] ($CDCl_3$) δ: 1.75—2.45 (6H, m, 3 × CH_2), 3.20—3.85 (6H, m, 2 × CH_3), 4.68—4.71 (2H, m, 3-H and 7-H), 7.12—7.58 (10H, m, aromatic H). ^{13}C-NMR ($CDCl_3$) δ: 21.84 (t), 24.94 (t), 52.33 (q), 63.93 (d), 127.38 (d), 127.50 (d), 128.41 (d), 131.07 (d), 133.32 (s), 169.63 (s), 170.94 (s). IR ν_{max}^{KBr} cm^{-1}: 1744 (C=O), 1652 (C=O). MS m/z: 424 (M^+). *Anal.* Calcd for $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 65.13; H, 5.63; N, 6.48.

Pyrazolidine-*trans*-3,5-dicarboxylic Acid (11a) Under an argon atmosphere, compound **10a** (300 mg, 0.76 mmol) was heated in AcOH (30 ml) and 6 N HCl (30 ml) at 100 °C for 24 h. After cooling, AcOH was removed from the reaction mixture under reduced pressure and the residual solution was washed with Et_2O (50 ml × 4) to remove the generated benzoic acid. The aqueous layer was concentrated under reduced pressure to give 171 mg of the *trans*-five-membered cyclic hydrazoacetic acid dihydrochloride (97%) as a pale yellow solid. Under an argon atmosphere, the obtained dihydrochloride salt was dissolved in a little water and the pH of the solution was adjusted to 4 with NH_4OH to give free **11a** (48 mg, 40%) as colorless prisms, mp 205—207 °C (dec.). ^{1}H-NMR (1 N DCl) δ: 2.38 (2H, t, J=7.3 Hz, 4-H), 4.57 (2H, t, J=7.3 Hz, 3- and 5-H). ^{13}C-NMR (1 N DCl) δ: 33.89 (t, 4-C), 60.47 (d, 3-C), 60.63 (d, 5-C), 172.12 (s, C=O). IR ν_{max}^{KBr} cm^{-1}: 3212, 2500, 1730 (C=O), 1592 (C=O). MS (FAB) m/z: 161 (M^++1). *Anal.* Calcd for $C_5H_8N_2O_4$: C, 37.50; H, 5.04; N, 17.49. Found: C, 37.33; H, 4.94; N, 17.48.

Perhydropyridazine-*trans*-3,6-dicarboxylic Acid (11b) Under an argon atmosphere, compound **10b** (2.00 g, 4.87 mmol) was heated in AcOH (100 ml) and 6 N HCl (100 ml) at 100 °C for 24 h. After cooling, AcOH was removed from the reaction mixture under reduced pressure and the residual solution was washed with Et_2O (100 ml × 4) to remove the generated benzoic acid. The aqueous layer was concentrated under reduced pressure to give 1.18 g of the *trans*-six-membered cyclic hydrazoacetic acid dihydrochloride (98%) as a pale yellow solid. Under an argon atmosphere, the obtained dihydrochloride salt was dissolved in a little water and the pH of the solution was adjusted to 4 with NH_4OH to give free **11b** (420 mg, 49%) as colorless needles, mp 238 °C (dec.). ^{1}H-NMR (1 N DCl) δ: 1.86—2.05 (2H, m, 4-Ha and 5-Ha), 2.31—2.38 (2H, m, 4-Hb and 5-Hb), 4.01—4.03 (2H, m, 3- and 6-H). ^{13}C-NMR (1 N DCl) δ: 24.70 (t), 56.88 (d), 172.01 (s). IR ν_{max}^{KBr} cm^{-1}: 3424, 3244, 1680 (br, C=O). MS m/z: 174 (M^+). *Anal.* Calcd for $C_6H_{10}N_2O_4$: C, 41.38; H, 5.79; N, 16.09. Found: C, 41.20; H, 5.77; N, 16.16.

1,2-Diazepane-*trans*-3,7-dicarboxylic Acid (11c) Under an argon atmosphere, compound **10c** (1.00 g, 2.36 mmol) was heated in AcOH (50 ml) and 6 N HCl (50 ml) at 100 °C for 24 h. After cooling, AcOH was removed from the reaction mixture under reduced pressure and the residual solution was washed with Et_2O (50 ml × 4) to remove the generated benzoic acid. The aqueous layer was concentrated under reduced pressure. Under an argon atmosphere, the residual pale yellow solid, which proved to contain a 10% **9c** by ^{1}H-NMR analysis, was dissolved in a little hot water and the solution was cooled to 5 °C to give **11c** (225 mg, 50%) as a white powder, mp 197 °C (dec.). ^{1}H-NMR (1 N DCl) δ 1.81—1.83 (2H, m, 5-H), 2.03—2.24 (4H, m, 4-H and 6-H), 4.18 (2H, dd, J=7.5, 6.1 Hz, 3- and 7-H). ^{13}C-NMR (1 N DCl) δ: 21.70 (t), 29.35 (t), 61.45 (d), 173.56 (s). IR ν_{max}^{KBr} cm^{-1}: 3046, 1714 (C=O), 1586 (br, C=O). MS (FAB) m/z: 189 (M^++1). *Anal.* Calcd for $C_7H_{12}N_2O_4$: C, 44.68; H, 6.43; N, 14.89. Found: C, 44.42; H, 6.27; N, 14.58.

***meso*-2,4-Diaminoglutaric Acid (12a)** The dihydrochloride salt of **9a** (1.15 g, 4.93 mmol) was dissolved in 2 N HCl (70 ml) and hydrogenated in the presence of PtO_2 (200 mg) under atmospheric pressure for 7 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give 2,4-diaminoglutaric acid dihydrochloride (1.15 g, 99%) as a white solid. The obtained dihydrochloride salt was dissolved

in a little water and pyridine was added to the solution. The resultant precipitate was separated by filtration and recrystallized from water to give free **12a** (663 mg, 83%) as colorless prisms, mp 250 °C (dec.). ^{1}H-NMR (1 N DCl) δ: 2.39—2.46 (1H, m, 3-Ha), 2.65—2.78 (1H, m, 3-Hb), 4.36 (2H, dd, J=6.8, 6.8 Hz, 2- and 4-H). ^{13}C-NMR (1 N DCl) δ: 30.85 (t), 50.54 (d), 171.17 (s). IR ν_{max}^{KBr} cm^{-1}: 3072, 1644 (C=O). MS (FAB) m/z: 163 (M^++1). *Anal.* Calcd for $C_5H_{10}N_2O_4$: C, 37.04; H, 6.22; N, 17.28. Found: C, 36.89; H, 6.42; N, 17.27.

***meso*-2,5-Diaminoadipic Acid (12b)** The dihydrochloride salt of **9b** (1.18 g, 4.78 mmol) was dissolved in 2 N HCl (70 ml) and hydrogenated in the presence of PtO_2 (200 mg) under atmospheric pressure for 9 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give 2,5-diaminoadipic acid dihydrochloride (1.19 g, 100%) as a white solid. The obtained dihydrochloride salt was dissolved in a little water and pyridine was added to the solution. The resultant precipitate was separated by filtration and recrystallized from water to give free **12b** (765 mg, 84%) as a white powder, mp 311 °C (dec.) [lit.,[14b] mp 331 °C (dec.)]. ^{1}H-NMR (1 N DCl) δ: 2.11—2.18 (4H, m, 2×CH_2), 4.18 (2H, br s, 2- and 5-H). ^{13}C-NMR (1 N DCl) δ: 26.48 (t), 52.95 (d), 171.60 (s). IR ν_{max}^{KBr} cm^{-1}: 3388, 1610 (C=O). MS (FAB) m/z: 177 (M^++1). *Anal.* Calcd for $C_6H_{12}N_2O_4 \cdot 4/5H_2O$: C, 37.82; H, 7.19; N, 14.70. Found: C, 37.70; H, 7.03; N, 14.69.

***meso*-2,6-Diaminopimelic Acid (12c)** Compound **8c** (100 mg, 0.25 mmol) was hydrogenated for debenzylation in AcOH (5 ml) and 2 N HCl (5 ml) in the presence of 20% $Pd(OH)_2$/C (15 mg) under a pressure of 4 atm for 18 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in 2 N HCl (5 ml) and hydrogenated in the presence of PtO_2 (10 mg) under a pressure of 4 atm for 24 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in 2 N HCl (5 ml) and the solution was heated at 100 °C for 4 h. The solution was concentrated under reduced pressure to give *meso*-diaminopimelic acid dihydrochloride (64 mg, 97%) as a white solid. The obtained dihydrochloride salt was dissolved in a little water and the pH of the solution was adjusted to 7 with 2 N NaOH. The resultant precipitate was separated by filtration and recrystallized from water–EtOH to give free **12c** (39 mg, 78%) as colorless needles, mp >300 °C (dec.). ^{1}H-NMR (1 N DCl) δ: 1.45—1.60 (1H, m, 4-Ha), 1.60—1.75 (1H, m, 4-Hb), 1.88—2.12 (4H, m, 3- and 5-H), 4.11 (2H, t, J=6.4 Hz, 2- and 6-H). ^{13}C-NMR (1 N DCl) δ: 21.20 (t), 39.97 (t), 53.30 (d), 172.21 (s). IR ν_{max}^{KBr} cm^{-1}: 3456, 3228, 1636 (C=O). MS (FAB) m/z: 191 (M^++1). *Anal.* Calcd for $C_7H_{14}N_2O_4 \cdot 1/2H_2O$: C, 42.21; H, 7.59; N, 14.06. Found: C, 42.44; H, 7.27; N, 14.03.

***meso*-2,7-Diaminosuberic Acid (12d)** Compound **8d** (100 mg, 0.24 mmol) was hydrogenated for debenzylation in AcOH (5 ml) and 2 N HCl (5 ml) in the presence of 20% $Pd(OH)_2$/C (15 mg) under a pressure of 4 atm for 18 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in 2 N HCl (5 ml) and hydrogenated in the presence of PtO_2 (10 mg) under a pressure of 4 atm for 24 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in 2 N HCl (5 ml) and the solution was heated at 100 °C for 4 h. The solution was concentrated under reduced pressure to give *meso*-diaminosuberic acid dihydrochloride (65 mg, 97%) as a white solid. The obtained dihydrochloride salt was dissolved in a little water and the pH of the solution was adjusted to 7 with 2 N NaOH. The resultant precipitate was separated by filtration and recrystallized from water–EtOH to give free **12d** (42 mg, 84%) as colorless prisms, mp >300 °C. ^{1}H-NMR (1 N DCl) δ: 1.34—1.59 (4H, m, 4- and 5-H), 1.85—2.05 (4H, m, 3- and 6-H), 4.09 (2H, t, J=6.2 Hz, 2- and 7-H). ^{13}C-NMR (1 N DCl) δ: 24.55 (t), 30.05 (t), 53.58 (d), 172.43 (s). IR ν_{max}^{KBr} cm^{-1}: 3444, 1656 (C=O). MS (FAB) m/z: 205 (M^++1). *Anal.* Calcd for $C_8H_{16}N_2O_4$: C, 47.05; H, 7.90; N, 13.72. Found: C, 46.79; H, 7.91; N, 13.69.

References and Notes

1) Achiwa K., Yamada S., *Tetrahedron Lett.*, **31**, 2701—2704 (1975).
2) Thiele J., Heuser K., *Ann.*, **290**, 1—43 (1896).
3) Thiele J., Bailey J., *Ann.*, **303**, 75—91 (1898).
4) Buchner E., Perkel L., *Chem. Ber.*, **36**, 3774—3782 (1903).
5) Gisin B., Brenner M., *Helv. Chim. Acta*, **53**, 1030—1043 (1970).
6) Ren Y., Jiang Z., Liu Z., Yu X., *Dalian Gongxueyuan Xuebao*, **25**, 75—80 (1986).
7) Simmonds D. H., *Biochem. J.*, **58**, 520—523 (1954).
8) *a*) Sturm P. A., Henry D. W., *J. Med. Chem.*, **17**, 481—487 (1974); *b*) Newman H., *J. Heterocycl. Chem.*, **11**, 449—451 (1974).
9) Williams R. M., Yuan C., *J. Org. Chem.*, **57**, 6519—6527 (1992).
10) Jurgens A. R., *Tetrahedron Lett.*, **33**, 4727—4730 (1992).
11) A part of this work was reported in a preliminary form; Arakawa Y., Goto T., Kawase K., Yoshifuji S., *Chem. Pharm. Bull.*, **43**, 535—536 (1995).
12) *a*) Mackay D., Marx U. F., Waters W. A., *J. Chem. Soc.*, **1964**, 4793—4800; *b*) Chung C. Y-J., Mackay D., Sauer T. D., *Can. J. Chem.*, **50**, 1568—1573 (1972); *c*) *Idem, ibid.*, **50**, 3315—3321 (1972).
13) Yoshifuji S., Tanaka K., Kawai T., Nitta Y., *Chem. Pharm. Bull.*, **33**, 5515—5521 (1985).
14) *a*) Carpino L. A., Terry P. H., Crowley P. J., *J. Org. Chem.*, **26**, 4336—4340 (1961); *b*) Carpino L. A., Terry P. H., Thatte S. D., *J. Org. Chem.*, **31**, 2867—2873 (1966).
15) Some signals split or broaden due to the rotamers or the conformers.