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Stereospecific synthesis of new 2,3,4,5-piperidinetetracarboxylic acids and 2,3,5-piperidinetricarboxylic acids

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Abstract—Diels–Alder adducts of 1,2-dihydropyridine with maleic and acrylic acid derivatives were stereospecifically converted by way of RuO_4 oxidation into new *r*-2,*c*-3,*c*-4,*c*-5-piperidinetetracarboxylic acid, *r*-2,*t*-3,*t*-4,*c*-5-piperidinetetracarboxylic acid, *r*-2,*c*-3,*c*-5-piperidinetricarboxylic acid, and *r*-2,*t*-3,*c*-5-piperidinetricarboxylic acid.

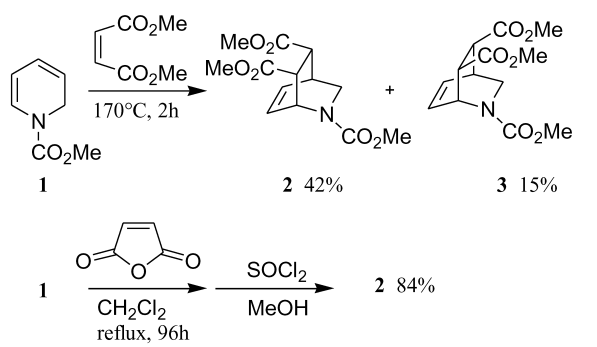
During our previous study of the synthesis of amino acids using Diels–Alder (D–A) adducts of dienes and *N*-containing dienophiles, we achieved a stereospecific synthesis of 2,5-piperidinedicarboxylic acid,[1] which was shown to act on the *N*-methyl-D-aspartate (NMDA) receptor. This gave rise to our present interest in the synthesis of piperidinepolycarboxylic acids with a *cis*-2,5-dicarboxy configuration. As distinct from our former method, we here chose D–A adducts (isoquinuclidines) of dienophiles and the *N*-containing dienes as the stereo-controlling materials to synthesize new 2,3,4,5-piperidine-tetracarboxylic and 2,3,5-piperidinetricarboxylic acids. D–A reactions of 1,2-dihydropyridines (DHPs), the characteristics of which suggest that they are components of isoquinuclidines, are widely used,[2] and a lack of *endo*–*exo* stereoselectivity is frequently observed, although, prior to the present work, no reasonable explanation for this phenomenon has been presented.

1. Results and discussion

First, we achieved the D–A reactions of *N*-methoxycarbonyl-1,2-dihydropyridine (Moc-DHP, **1**)[3] with several carboxylic acid derivatives. Moc-DHP reacted with dimethyl maleate to give *endo*-**2** and *exo*-**3** in 42 and 15% yields. Employment of maleic anhydride as a dienophile followed by treatment with $SOCl_2$–MeOH gave only **2** in 84% yield (Scheme 1).

With methyl acrylate, Moc-DHP reacted to give *endo*-**4a** and *exo*-**5a** in the ratios given in Table 1 i.e. ca. 1:1 under every condition, with *endo*-**2** being major; although Campbell et al. have reported a similar reaction as being somewhat *exo*-selective.[4] The use of 2-phenoxyethyl and benzyl acrylates resulted in a slight increase in the amount of D–A adducts in the *endo*-ratios. At these temperatures, *endo*- and *exo*-D–A adducts did not isomerize into each other; because these isolated D–A adducts were treated with a corresponding maleate or acrylate, no formation of their stereoisomers was observed and the recoveries of the D–A adducts were almost quantitative, respectively. Thus the D–A reactions appear to be kinetically controlled.

Overman et al. have reported that D–A reactions of *trans*-1-*N*-acylamino-1,3-butadienes, which are (*E*)-carbamoyldienes, with methyl acrylate are *endo*-selective (80%), and that the stereoselectivity can be attributed to the secondary orbital interaction between the frontier molecular orbitals.[5] Moc-DHP, however, is a (*Z*)-carbamoyldiene, so the



Scheme 1. Diels–Alder reaction of 1,2-dihydropyridine with maleic acid derivatives.

Keywords: 1,2-dihydropyridine; 2,3,4,5-piperidinetetracarboxylic acid; 2,3,5-piperidinetricarboxylic acid; Diels–Alder adduct; ruthenium tetroxide.

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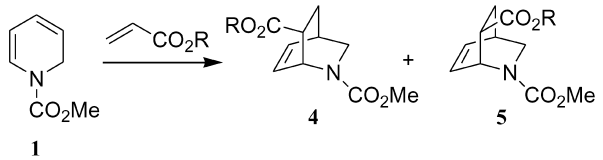
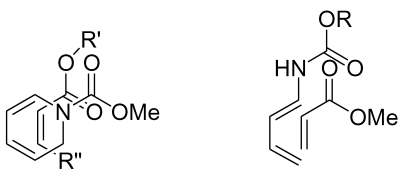
Table 1. Diels–Alder reaction of 1,2-dihydropyridine with acrylic acid esters



Entry	R	Reaction conditions	Products		Yield (%)[a]	
			endo	*exo*	*endo*	*exo*
1	Me	100°C, 120 h	**4a**	**5a**	33	30
2		Xylene, reflux, 120 h[b]			37	28
3		160°C, 33 h			44	31
4	$PhOCH_2CH_2$	100°C, 60 h	**4b**	**5b**	20	11
5		Xylene, reflux, 15 h[b]			19	10
6		160°C, 15 h			22	12
7	Bn	Xylene, reflux, 15 h[b]	**4c**	**5c**	26	13
8		160°C, 15 h			28	15

[a] Isolated yields, but confirmed by ^{1}H NMR and HPLC analyses of the reaction mixtures.
[b] The concentrations of both **1** and the acrylates were 1.8 M.

urethane–ester interaction must not be negligible based on the D–A reactions of DHPs. The molecular orbital calculation using the MOPAC AM1 method[6] suggests that the *exo*-forming overlap between the HOMO of Moc-DHP and the LUMO of methyl acrylate causes discord in the coefficient signs between the *N*-atom and the *C*-atom of the ester carbonyl group; the secondary orbital interaction seems not to contribute to the formation of the *exo*-D–A adduct. Therefore, the urethane–ester interaction probably consist of an electrostatic attraction between the *N*-atom and the *C*-atom of the ester carbonyl group, and an electrostatic attraction between the *C*-atom at the carbamoyl group and the *O*-atom at the ester carbonyl group (**A** in Fig. 1). The latter attraction may also exist in the case of (*E*)-carbamoyldienes that take on the conformation (**B** in Fig. 1).



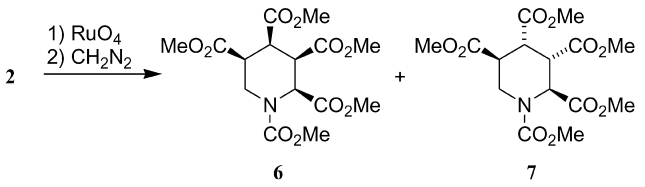
A **B**

Figure 1. *exo*-Forming transition states of the Diels–Alder reactions of (*Z*)-carbamoyldiene (**A**) and (*E*)-carbamoyldiene (**B**).

This explanation would also account for the steric hindrance between another carbonyl group of the maleic acid derivative and DHP's methylene, as well as the decrease in the formation of the *exo*-isomers by the bulky alkyl group of the ester.

When the oxidation of compound **2** with RuO_4 ($RuO_2{\cdot}xH_2O$, AcOEt, 10% $NaIO_4$ aq.) was achieved at room temperature, subsequent treatment of the product with diazomethane afforded a mixture of the isomers **6** and **7**. At lower temperatures, the isomerization decreased (Table 2). In the RuO_4 oxidation reactions employing AcOEt as a solvent, the AcOEt layers usually look yellow, the color of RuO_4,

Table 2. Oxidation of **2** with RuO_4

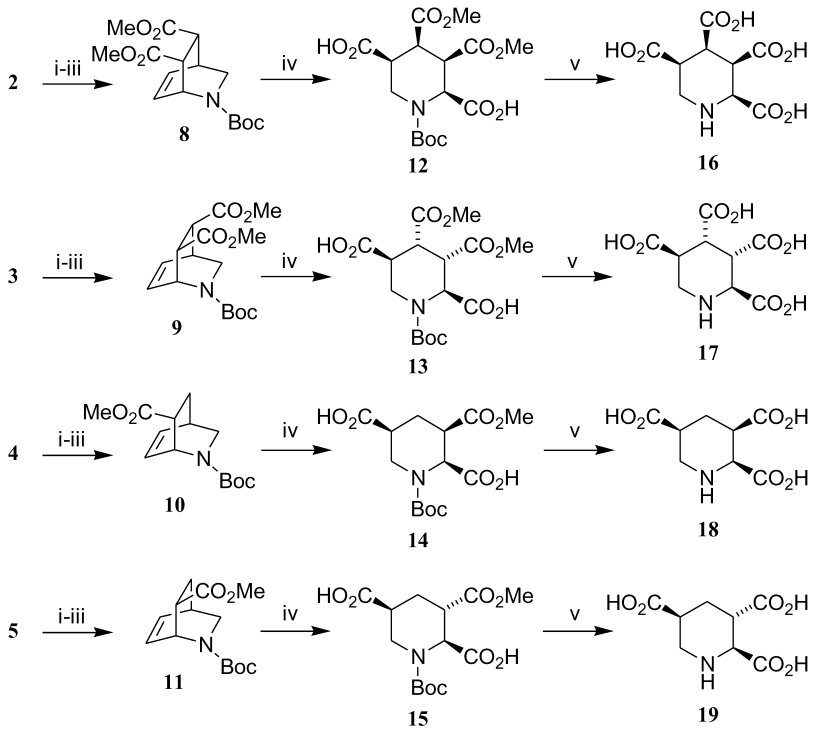


Reaction conditions		Yield (%)	
Temp (°C)	Time (h)	**6**	**7**
0	51	84	2
10	31	26	57
15	18	14	67
20	18	12	72

but in the present cases, the AcOEt layers looked orange-brown at the early time of the reactions, and after the disappearance of **2**, the color turned yellow.

Oxidation of **2** with ozone followed by treatments with performic acid and with diazomethane gave **6** in 51% yield; however, no formation of **7** was observed in this case. Oxidation of **3** with RuO_4 at 0°C for 14 h followed by treatment with diazomethane also afforded a mixture of the isomers **6** and **7** in 0.1 and 71% yields. Given that no other stereoisomers were formed, this new isomerization cannot be explained unless a retro-D–A reaction occurred under the oxidation conditions, since another process for isomerization should accompany the formation of the other stereoisomers, e.g., 3,4-*trans*-diesters. We believe that RuO_4 behaved as a Lewis acid, catalyzing not only the Diels–Alder reaction but also its reverse reaction. Although the disappearance of **2** under the RuO_4 oxidation condition at 0°C required 30 h, the disappearance of **3** under the similar condition required 1 h, analyzed by the thin-layer chromatography on silica gel. The much faster rate of the oxidation of **3** than that of **2** seems to be a main reason why compound **7** was the major product in the case of the RuO_4 oxidation of **2** at higher temperature. Treatment of these isolated products **6** and **7** with 6 M HCl at temperatures over 50°C resulted in the formation of some stereoisomers of the target, and treatment at 50°C resulted in an incomplete hydrolysis of urethane and/or ester functions. Therefore, before RuO_4 oxidation, the *N*-Moc group should have been converted to an *N*-Boc group which can be easily removed under the acidic condition. We did not employ Boc-DHP as a starting material, because it is not easy to be synthesized[2d] and *N*-Boc group seems to be unstable at the following steps.

The *N*-Moc groups of the isolated D–A adducts **2**–**5** were eliminated with Me_3SiI and were then converted to *N*-Boc methyl esters **8**–**11** in the usual manner in 89, 82, 84, and 83% yields, respectively (Scheme 2). Oxidation of olefins **8**–**11** with RuO_4 ($RuO_2{\cdot}xH_2O$, AcOEt, 10% $NaIO_4$ aq., 0°C) afforded dicarboxylic acids **12**–**15**. In these cases, there was no isomerization comparable to that in the oxidation of **2**, which suggested that the proximity of RuO_4 to the urethane group may be required to cause the isomerization. Compound **12** was treated with diazomethane to afford tetramethyl ester **12′**, and attempts were made to hydrolyze this product. Similarly to the hydrolysis of **6** and **7**,



Scheme 2. Conversion of Diels–Alder adducts into the amino acids. *Reagents and conditions*: (i) Me_3SiI, CCl_4, room temp, 4 days, then H_2O; (ii) $SOCl_2$, MeOH; (iii) Boc_2O, Et_3N, $CHCl_3$; (iv) $RuO_2{\cdot}xH_2O$, 10% $NaIO_4$ aq., AcOEt, 0°C; (v) 6 M HCl, 50°C.

treatment of **12′** with 6 M HCl at temperatures over 50°C resulted in the formation of some stereoisomers of the target, and treatment at 50°C resulted in an incomplete hydrolysis of ester functions. We therefore concluded that **12**–**15** were purified and directly hydrolyzed. Fortunately, **12** and **13** could be purified by recrystallization in 90 and 84% yields, and **14** and **15** could be purified by silica gel column chromatography in 97 and 97% yields, respectively. These purified dicarboxylic acids were then heated in 6 M HCl at 50°C, producing the new amino acids, *r*-2,*c*-3,*c*-4,*c*-5-piperidinetetracarboxylic acid (**16**), *r*-2,*t*-3,*t*-4,*c*-5-piperidinetetracarboxylic acid (**17**), *r*-2,*c*-3,*c*-5-piperidinetricarboxylic acid (**18**), and *r*-2,*t*-3,*c*-5-piperidinetricarboxylic acid (**19**), respectively. ^{1}H NMR monitoring revealed that completion of the hydrolysis required 3 weeks in the case of **12**, 3 weeks in the case of **13**, 13 d in the case of **14**, and 3 d in the case of **15**. These target amino acids were quantitatively obtained as hydrochlorides. Free amino acid **16** was obtained as a crystal in 90% yield by adjusting the pH of its hydrochloride's aqueous solution to 4. When the hydrochlorides of **17**–**19** were treated similarly, monohydrates of **17** and **19** were obtained as crystals in 91 and 90% yields, respectively, but **18**·HCl could not be desalted. Compound **18**·HCl was therefore treated with propylene oxide to give free **18** as a powder in 91% yield.

The stereochemistries of the amino acids were confirmed by observation of the coupling constants and the nuclear Overhauser effects (NOE, measured in differential modes) of the ^{1}H NMR analysis. Compounds **16**, **18**, and **19** existed mainly as the conformation indicated in Fig. 2 in 2 M DCl. For **16**, as the coupling constant between H^2 and H^3 was 3.7 Hz and H^2 had NOEs between H^3, H^4, and H^{6a}, the relative configuration proved to be 2,3-*cis* and 2,4-*cis*. Because the signals of H^4 and H^5 overlapped, no pertinent NOE data for elucidation of the 5-position was obtained; however, the coupling constant between H^5 and H^{6a} was 2.2 Hz and that between H^5 and H^{6b} was 4.4 Hz. This

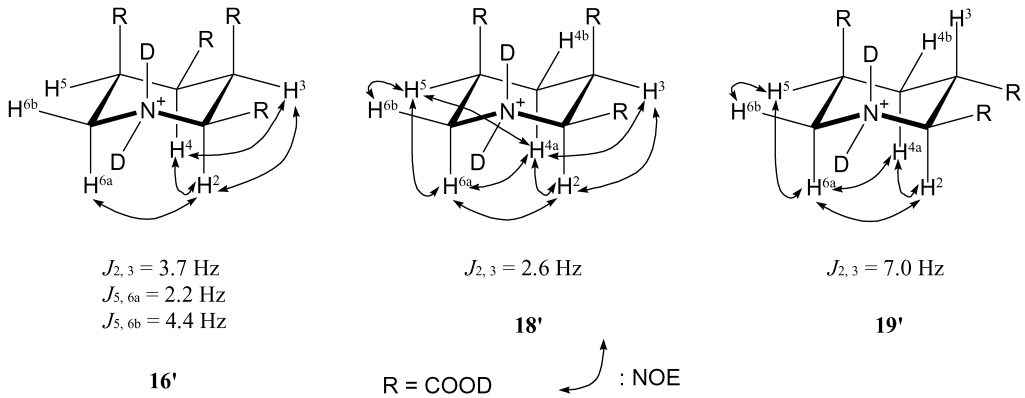


Figure 2. Selected decisive coupling constants and NOE relationships of the target amino acids **16**, **18**, and **19** in 2 M DCl (**16′**, **18′**, and **19′**).

implies that H^5 is situated at *equatorial*, 2,5-*cis*. For **18**, a result similar to that for **16** was obtained; furthermore, H^5 was shown to be located in close proximity to H^{4a}, H^{6a}, and H^{6b}, indicating 2,3-*cis* and 2,5-*cis*. Although the conformation **18′** in Fig. 2 appeared to be unstable because of the 1,3-*diaxial* interaction, it was actually stable because of the possible intramolecular hydrogen bonds between two *axial* carboxy groups and an *axial* N-D. For **19**, although the NOE relationships resembled those of **18**, the coupling constant between H^5 and H^{6a} was 7.0 Hz, indicating 2,3-*trans* and 2,5-*cis*. Compound **17** seemed to exist as two chair conformations, because the signal of H^2 split into four signals despite the fact that the H–H COSY spectra corresponded to H^2, indicating that there was no coupling between any proton other than H^3. No decisive NOE was observed because the signals of H^3, H^4, and H^5 overlapped; however, none of analytical data were in contradiction with the structure **17**.

Thus we succeeded in stereospecifically synthesizing new 2,3,4,5-piperidinetetracarboxylic acids **16** and **17**, and 2,3,5-piperidinetricarboxylic acids **18** and **19**, from Diels–Alder adducts.

2. Experimental

2.1. General

Melting points were measured with a Yanagimoto micro-melting point apparatus and are uncorrected. NMR spectra, except for those of the amino acids, were recorded in chloroform-d ($CDCl_3$) or acetone-d_6 on a GSX-400 spectrometer (JEOL, Tokyo, Japan) using tetramethylsilane as an internal standard. For the amino acids, analysis was performed in 2 M deuterium chloride (DCl) using 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 (Hitachi, Tokyo, Japan). Mass spectra (MS) were obtained with a JEOL JMS-DX300 spectrometer (JEOL, Tokyo, Japan). Column chromatography was performed on silica gel (Kieselgel 60, 70–230 mesh, Merck, Darmstadt, Germany). Flash chromatography was performed on silica gel (Silica Gel 60, 230–400 mesh, Nacalai Tesque, Kyoto, Japan).

2.1.1. Trimethyl (1*R* *,4*S* *,5*R* *,6*R* *)-2-azabicyclo[2.2.2]-oct-7-ene-2,5,6-tricarboxylate (2) and trimethyl (1*R* *,4*S* *,5*S* *,6*S* *)-2-azabicyclo[2.2.2]oct-7-ene-2,5,6-tricarboxylate (3). Using dimethyl maleate: A mixture of 1,2-dihydropyridine **1** (20.95 g, 150.6 mmol) and dimethyl maleate (26.51 g, 183.9 mmol) was heated in a sealed tube at 170°C (oil bath temp) for 2 h. The reaction mixture was subjected to flash chromatography [hexane–Et_2O (3:1, then 1:1)] to give a white solid, which was recrystallized from *i*-Pr_2O, giving **3** (5.56 g, 13%) as colorless needles, mp 105–106°C. The following eluate afforded **2** (17.41 g, 41%) as a colorless oil.

Using maleic anhydride: A solution of **1** (15.00 g, 107.8 mmol) and maleic anhydride (10.58 g, 107.9 mmol) in CH_2Cl_2 (100 ml) was refluxed for 4 d, and the mixture was concentrated under reduced pressure to give a yellow oil. Thionyl chloride (25.70 g, 216.0 mmol) was added dropwise to MeOH (100 ml) at −10°C, and the mixture was stirred at room temperature for 30 min. The yellow oil obtained previously was dissolved in MeOH (20 ml), which was added to the $SOCl_2$–MeOH solution, and the whole was stirred overnight. The reaction mixture was concentrated under reduced pressure. MeOH (100 ml) was added to the residue and the solution was concentrated under reduced pressure; this operation was then repeated twice. The residue was dissolved in $CHCl_3$ (200 ml), washed with sat. $NaHCO_3$ (100 ml×2) and water (100 ml×2). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a brown-red oil. It was subjected to flash chromatography [hexane–Et_2O (3:1, then 1:1)] to give **2** (25.67 g, 84%). **2**: ^{1}H NMR[7] ($CDCl_3$) δ: 2.98 (1H, dd, *J*=10.3, 2.2 Hz, 3-Ha), 3.13 (2H, t, *J*=10.1 Hz, 4- and 5-H), 3.31 (1H, d, *J*=10.3 Hz, 3-Hb), 3.41–3.50 (1H, m, 6-H), 3.62, 3.63, and 3.64 (6H, each s, 2× OCH_3), 3.69 and 3.72 (3H, each s, OCH_3), 4.94 and 5.09 (1H, each br, 1-H), 6.48–6.50 (2H, m, olefinic H); ^{13}C NMR[7] ($CDCl_3$) δ: 33.62 (d), 33.68 (d), 44.51 (d), 44.59 (d), 46.89 (t), 47.07 (d), 47.10 (t), 47.37 (d), 48.48 (d), 51.76 (q), 51.91 (q), 52.60 (q), 130.84 (d), 131.16 (d), 132.79 (d), 132.94 (d), 155.25 (s), 155.69 (s), 170.84 (s), 170.92 (s), 172.42 (s), 172.50 (s); IR (neat): 1750 (C═O), 1708 (C═O) cm^{-1}; HRMS calcd for $C_{13}H_{17}NO_6$ (M^+): 283.1056, found 283.1056. **3**: ^{1}H NMR[7] ($CDCl_3$) δ: 2.96–3.05 (2H, m, 3-Ha and 4-H), 3.25–3.27 (1H, m, 5-H), 3.34 (1H, dd, *J*=4.8, 2.2 Hz, 3-Hb), 3.41 (1H, d, *J*=10.3 Hz, 6-H), 3.64 and 3.67 (6H, each s, 2× OCH_3), 3.72 and 3.74 (3H, each s, OCH_3), 5.00 and 5.12 (1H, each d, *J*=5.9 Hz, 1-H), 6.35–6.39 and 6.47–6.54 (2H, m, olefinic H); ^{13}C NMR[7] ($CDCl_3$) δ: 33.08 (d), 33.18 (d), 42.35 (d), 42.52 (d), 46.34 (t), 46.74 (t), 48.06 (q), 48.15 (d), 48.19 (d), 48.57 (d), 52.32 (q), 52.57 (q), 132.53 (d), 132.83 (d), 133.00 (d), 155.54 (s) 156.07 (s), 172.22 (s), 172.65 (s), 173.28 (s); IR (KBr): 1734 (C═O), 1696 (C═O) cm^{-1}; MS *m/z*: 283 (M^+). Anal. calcd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05; N, 4.94. Found: C, 55.16; H, 5.92; N, 4.94.

2.1.2. Dimethyl (1*R* *,4*R* *,6*R* *)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (4a) and dimethyl (1*R* *,4*R* *,6*S* *)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (5a). A mixture of 1,2-dihydropyridine **1** (750 mg, 5.39 mmol) and methyl acrylate (6.19 g, 71.9 mmol) was heated in a sealed tube at 160°C (oil bath temp) for 33 h. The reaction mixture was dissolved in AcOEt (50 ml), and washed with water (30 ml×3). The AcOEt layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual oil was subjected to column chromatography on silica gel [$CHCl_3$–Et_2O (20:1)] to give **4a** (534 mg, 44%) as a colorless oil, and then **5a** (380 mg, 31%) as a colorless oil. **4a**: ^{1}H NMR[7] ($CDCl_3$) δ: 1.86 (2H, m, 5-H), 2.84 (1H, br s, 4-H), 2.91–2.98 (1H, m, 3-Ha), 3.06–3.08 (1H, m, 6-H), 3.25–3.28 (1H, m, 3-Hb), 3.66–3.72 (6H, m, 2× OCH_3), 5.01 and 5.17 (1H, each s, 1-H), 6.27–6.29 and 6.42–6.48 (2H, m, olefinic H); ^{13}C NMR[7] ($CDCl_3$) δ: 26.02 (t), 30.42 (d), 30.67 (d), 43.76 (d), 44.02 (d), 46.71 (d), 47.04 (t), 47.13 (d), 47.38 (t), 51.90 (q), 51.94 (q), 52.41 (q), 52.47 (q),130.18 (d), 130.67 (d), 135.08 (d), 135.49 (d), 155.35 (s), 155.83 (s), 173.09 (s), 173.16 (s); IR (neat): 1736 (C═O), 1699 (C═O) cm^{-1}; HRMS calcd for $C_{11}H_{15}NO_4$ (M^+): 225.1001, found 225.1000. **5a**: ^{1}H NMR[7] ($CDCl_3$) δ: 1.52–1.63 (1H, m, 5-Ha), 2.07–2.13 (1H, m, 5-Hb),

2.53–2.60 (1H, m, 6-H), 2.78–2.82 (1H, m, 4-H), 2.94–3.02 (1H, m, 3-Ha), 3.35–3.39 (1H, m, 3-Hb), 3.60–3.75 (6H, m, 2× OCH_3), 4.89–4.91 and 5.02–5.04 (1H, m, 1-H), 6.42–6.50 (2H, m, olefinic H); ^{13}C NMR[7] ($CDCl_3$) δ: 24.94 (t), 25.09 (t), 30.04 (d), 30.26 (d), 44.12 (d), 44.40 (d), 47.26 (t), 47.68 (t), 47.95 (d), 48.37 (d), 51.93 (q), 52.13 (q), 52.34 (q), 131.65 (d), 132.15 (d), 135.05 (d), 135.36 (d), 155.61 (s), 156.18 (s), 173.61 (s), 173.95 (s); IR (neat): 1738 (C═O), 1699 (C═O) cm^{-1}; HRMS calcd for $C_{11}H_{15}NO_4$ (M^+): 225.1001, found 225.1001.

2.1.3. 2-Methyl 6-(2-phenoxyethyl) (1*R,4*R**,6*R**)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (4b) and 2-methyl 6-(2-phenoxyethyl) (1*R**,4*R**,6*S**)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (5b).** A mixture of 1,2-dihydropyridine **1** (37.95 g, 273 mmol) and 2-phenoxyethyl acrylate (67.5 g, 351 mmol) was heated in a sealed tube at 160°C (oil bath temp) for 15 h. The reaction mixture was subjected to flash chromatography [hexane–Et_2O (3:1, then 1:1)] to give **5b** (10.60 g, 12%) as a colorless oil, and then **4b** (19.45 g, 22%) as a colorless oil. **4b**: ^1H NMR[7] ($CDCl_3$) δ: 1.85–1.87 (2H, m, 5-H), 2.82 (1H, br s, 4-H), 2.89–2.96 (1H, m, 3-Ha), 3.07–3.15 (1H, m, 6-H), 3.25 (1H, m, 3-Hb), 3.67 and 3.71 (3H, each s, N–$COOCH_3$), 4.13–4.17 and 4.34–4.46 (4H, m, OCH_2CH_2O), 5.01 and 5.19 (1H, each s, 1-H), 6.26–6.44 (2H, m, olefinic H), 6.89–6.99 and 7.27–7.29 (5H, m, aromatic H); ^{13}C NMR[7] ($CDCl_3$) δ: 26.03 (t), 30.37 (d), 30.62 (d), 43.85 (d), 44.11 (d), 46.69 (d), 47.10 (t and d), 47.42 (t), 52.43 (q), 52.47 (q), 63.04 (t), 63.15 (t), 65.67 (t), 65.76 (t), 114.63 (d), 121.16 (d), 121.25 (d), 129.52 (d), 130.22 (d), 130.74 (d), 134.99 (d), 135.41 (d), 155.37 (s), 155.83 (s), 158.44 (s), 172.67 (s); IR (neat): 1736 (C═O), 1699 (C═O) cm^{-1}; HRMS calcd for $C_{18}H_{21}NO_5$ (M^+): 331.1420, found 331.1419. **5b**: ^1H NMR[7] ($CDCl_3$) δ: 1.53–1.59 (1H, m, 5-Ha), 2.07–2.12 (1H, m, 5-Hb), 2.58–2.65 (1H, m, 6-H), 2.77–2.81 (1H, m, 4-H), 2.93–3.02 (1H, m, 3-Ha), 3.35–3.40 (1H, m, 3-Hb), 3.58 and 3.60 (3H, m, N–$COOCH_3$), 4.13–4.24 and 4.42–4.46 (4H, m, OCH_2CH_2O), 4.94–4.95 and 5.06–5.07 (1H, m, 1-H), 6.41–6.47 (2H, m, olefinic H), 6.93–6.99 and 7.26–7.32 (5H, m, aromatic H); ^{13}C NMR[7] ($CDCl_3$) δ: 24.92 (t), 25.06 (t), 30.24 (d), 30.33 (d), 44.26 (d), 44.43 (d), 47.25 (t), 47.63 (t), 47.98 (d), 48.38 (d), 52.34 (q), 63.24 (t), 63.28 (t), 65.74 (t), 65.83 (t), 114.62 (d), 114.68 (d), 121.04 (d), 121.21 (d), 129.46 (d), 129.55 (d), 131.65 (d), 132.10 (d), 135.03 (d), 135.34 (d), 155.66 (s), 156.21 (s), 158.52 (s), 158.56 (s), 173.10 (s), 173.44 (s); IR (neat): 1736 (C═O), 1693 (C═O) cm^{-1}; HRMS calcd for $C_{18}H_{21}NO_5$ (M^+): 331.1420, found 331.1417.

2.1.4. 6-Benzyl 2-methyl (1*R,4*R**,6*R**)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (4c) and 6-benzyl 2-methyl (1*R**,4*R**,6*S**)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (5c).** A mixture of 1,2-dihydropyridine **1** (37.95 g, 273 mmol) and benzyl acrylate (57.0 g, 351 mmol) was heated in a sealed tube at 160°C (oil bath temp) for 15 h. The reaction mixture was subjected to flash chromatography [hexane–Et_2O (4:1, then 2:1)] to give **5c** (12.33 g, 15%) as a colorless oil, and then **4c** (23.02 g, 28%) as a colorless oil. **4c**: ^1H NMR[7] ($CDCl_3$) δ: 1.87–1.91 (2H, m, 5-H), 2.82 (1H, br s, 4-H), 2.90–2.97 (1H, m, 3-Ha), 3.07–3.15 (1H, m, 6-H), 3.25 (1H, m, 3-Hb), 3.63 and 3.70 (3H, each s, N–$COOCH_3$), 5.02–5.20 (3H, m, OCH_2Ph and 1-H), 6.25–6.30 and 6.39–6.45 (2H, m, olefinic H), 7.33–7.36 (5H, m, aromatic H); ^{13}C NMR[7] ($CDCl_3$) δ: 26.02 (t), 26.14 (t), 30.42 (d), 30.65 (d), 43.96 (d), 44.25 (d), 46.74 (d), 47.08 (t), 47.12 (d), 47.40 (t), 52.41 (q), 52.47 (q), 66.53 (t), 66.62 (t), 128.14 (d), 128.22 (d), 128.28 (d), 128.32 (d), 128.40 (d), 128.54 (d), 130.21 (d), 130.66 (d), 135.05 (d), 135.43 (d), 135.85 (s), 155.36 (s), 155.83 (s), 172.46 (s); IR (neat): 1738 (C═O), 1693 (C═O) cm^{-1}; HRMS calcd for $C_{17}H_{19}NO_4$ (M^+): 301.1314, found 301.1313. **5c**: ^1H NMR[7] ($CDCl_3$) δ: 1.53–1.63 (1H, m, 5-Ha), 2.09–2.17 (1H, m, 5-Hb), 2.57–2.63 (1H, m, 6-H), 2.77–2.81 (1H, m, 4-H), 2.94–3.03 (1H, m, 3-Ha), 3.35–3.40 (1H, m, 3-Hb), 3.55 and 3.63 (3H, m, N–$COOCH_3$), 4.95–5.18 (3H, m, OCH_2Ph and 1-H), 6.41–6.49 (2H, m, olefinic H), 7.26–7.42 (5H, m, aromatic H); ^{13}C NMR[7] ($CDCl_3$) δ: 24.99 (t), 25.12 (t), 30.07 (d), 30.27 (d), 44.35 (d), 44.55 (d), 47.30 (t), 47.63 (t), 48.00 (d), 48.38 (d), 52.32 (q), 52.35 (q), 66.76 (t), 67.05 (t), 128.17 (d), 128.22 (d), 128.25 (d), 128.46 (d), 128.51 (d), 128.57 (d), 131.68 (d), 132.21 (d), 134.99 (d), 135.34 (d), 135.88 (s), 135.93 (s), 155.63 (s), 156.19 (s), 172.98 (s), 173.38 (s); IR (neat): 1736 (C═O), 1693 (C═O) cm^{-1}; HRMS calcd for $C_{17}H_{19}NO_4$ (M^+): 301.1314, found 301.1320.

2.1.5. Pentamethyl 1,*r*-2,*c*-3,*c*-4,*c*-5-piperidinepentacarboxylate (6). Using RuO_4: A solution of **2** (400 mg, 1.41 mmol) in AcOEt (25 ml), $RuO_2{\cdot}xH_2O$ (4 mg), and a 10% $NaIO_4$ aqueous solution (17 ml) were mixed and then vigorously stirred at 0°C for 51 h. The AcOEt layer was separated, and the aqueous layer was extracted with AcOEt (50 ml×6). Isopropyl alcohol (1 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 (20 ml) and treated with diazomethane. The solution was concentrated, and the residual gray oil was subjected to column chromatography on silica gel [hexane–AcOEt (3:1)] to give a white solid. It was recrystallized from i-Pr_2O to give **6** (430 mg, 84%) as colorless prisms, mp 108–109°C.

Using ozone: Ozone gas (3–4% in air) was bubbled into a solution of **2** (1.00 g, 3.53 mmol) in MeOH (25 ml) at −75°C for 1 h with stirring. After the reaction mixture was warmed to room temperature, it was concentrated under reduced pressure. To the residue was added 90% formic acid (3.5 ml) and 30% H_2O_2 (1.7 ml), and the mixture was heated under gentle reflux for 2 h. The mixture was concentrated under reduced pressure to give a pale yellow oil, which was dissolved in MeOH (20 ml) and treated with diazomethane. The solution was concentrated under reduced pressure, and the residual yellow oil was subjected to column chromatography on silica gel [hexane–AcOEt (4:1)] to give a white solid. It was recrystallized from i-Pr_2O to give **6** (670 mg, 51%). ^1H NMR[7] ($CDCl_3$) δ: 2.68–2.72 (1H, m, 5-H), 3.02 (1H, t, J=5.5 Hz, 3-H), 3.38–3.54 (2H, m, 4-H and 6-Ha), 3.66 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.73–3.79 (9H, m, 3×OCH_3), 4.21 and 4.33 (1H, each dd, J=13.9, 3.6 Hz, 6-Hb), 5.25 and 5.43 (1H, d, J=5.9 Hz, 2-H); ^{13}C NMR[7] ($CDCl_3$) δ: 38.22 (t), 38.52 (t), 39.88 (d), 43.18 (d), 43.35 (d), 44.79 (d), 45.10 (d), 52.11 (q), 52.17 (q), 52.34 (q), 52.47 (q), 52.63 (d), 53.07 (d), 53.34 (q), 155.74 (s) 156.18 (s), 168.79

(s), 169.78 (s), 170.70 (s), 171.14 (s); IR (KBr): 1746 (C═O), 1714 (C═O) cm^{-1}; MS *m/z*: 375 (M^+). Anal. calcd for $C_{15}H_{21}NO_{10}$: C, 48.00; H, 5.64; N, 3.73. Found: C, 48.08; H, 5.48; N, 3.92.

2.1.6. Pentamethyl 1,*r*-2,*t*-3,*t*-4,*c*-5-piperidinepentacarboxylate (7). A solution of **2** (300 mg, 1.06 mmol) in AcOEt (20 ml), $RuO_2 \cdot xH_2O$ (3 mg), and a 10% $NaIO_4$ aqueous solution (13 ml) were mixed and then vigorously stirred at 0°C for 14 h. The AcOEt layer was separated, and the aqueous layer was extracted with AcOEt (40 ml×6). Isopropyl alcohol (1 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 (20 ml) and treated with diazomethane. The solution was concentrated, and the residual gray oil was subjected to column chromatography on silica gel [hexane–AcOEt (6:1, then 3:1)] to give a white solid. It was recrystallized from AcOEt–hexane to give **7** (284 mg, 71%) as colorless prisms, mp 105–106°C. ^{1}H NMR[7] ($CDCl_3$) δ: 2.76–2.79 and 2.84–2.89 (1H, m, 5-H), 3.44–3.59 (2H, m, 3-H and 6-Ha), 3.66 (3H, s, OCH_3), 3.71 (6H, s, 2×OCH_3), 3.74–3.89 (7H, m, 2×OCH_3 and 4-H), 4.33 and 4.47 (1H, each dd, *J*=13.4, 4.5 Hz, 6-Hb), 5.43 and 5.53 (1H, s, 2-H); ^{13}C NMR[7] ($CDCl_3$) δ: 38.37 (d), 38.49 (d), 38.77 (t), 39.00 (t), 39.15 (d), 42.50 (d), 42.96 (d), 52.11 (q), 52.31 (q), 52.82 (q), 53.08 (q), 53.28 (q), 53.63 (d), 53.90 (d), 156.12 (s) 156.57 (s), 169.91 (s), 170.02 (s), 170.90 (s), 171.16 (s), 171.30 (s), 172.09 (s); IR (KBr): 1732 (C═O), 1728 (C═O), 1724 (C═O), 1716 (C═O) cm^{-1}; MS *m/z*: 375 (M^+). Anal. calcd for $C_{15}H_{21}NO_{10}$: C, 48.00; H, 5.64; N, 3.73. Found: C, 48.16; H, 5.49; N, 3.86.

2.1.7. 2-*tert*-Butyl 5,6-dimethyl (1*R,4*S**,5*R**,6*R**)-2-azabicyclo[2.2.2]oct-7-ene-2,5,6-tricarboxylate (8).** Under an argon atmosphere, trimethylsilyl iodide (10.61 g, 53.03 mmol) was added to a solution of **2** (5.00 g, 17.7 mmol) in CCl_4 (100 ml) at 0°C and the mixture was stirred in the dark at room temperature for 4 d. After the reaction mixture was cooled in an ice bath, water was added (100 ml) and the mixture was vigorously stirred for 1 h. The aqueous layer was separated, washed with $CHCl_3$ (100 ml×5) and benzene (100 ml), and concentrated under reduced pressure, giving a yellowish brown oil. Thionyl chloride (4.63 g, 38.9 mmol) was added dropwise to MeOH (300 ml) at −10°C, and the mixture was stirred at room temperature for 30 min. The yellowish brown oil obtained previously was dissolved in MeOH (30 ml), which was added to the $SOCl_2$–MeOH solution, and the whole was stirred for 2 d. The reaction mixture was concentrated under reduced pressure. MeOH (100 ml) was added to the residue and the solution was concentrated under reduced pressure; this operation was then repeated 3 times. After the residue was dissolved in $CHCl_3$ (200 ml), triethylamine (2.68 g, 26.5 mmol) was added dropwise at 0°C, then Boc_2O (4.63 g, 21.2 mmol) was added. The mixture was stirred in the dark at room temperature for 4 d, and concentrated under reduced pressure. $CHCl_3$ (200 ml) and water (100 ml) were added to the residue and the whole was stirred for a few minutes, after which the insoluble material was filtered out using Hyflo Super-Cel®. The organic layer was washed with water (100 ml×3), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellowish brown oil. It was subjected to column chromatography on silica gel [hexane–Et_2O (2:1)] to give **8** (5.11 g, 89%) as a colorless oil. ^{1}H NMR[7] ($CDCl_3$) δ: 1.44 and 1.47 (9H, each s, $C(CH_3)_3$), 2.90–2.97 (1H, m, 3-Ha), 3.10–3.16 (2H, m, 4- and 5-H), 3.27 (1H, dd, *J*=10.6, 1.8 Hz, 3-Hb), 3.39–3.49 (1H, m, 6-H), 3.61 and 3.63 (6H, each s, 2×OCH_3), 4.86 and 5.06 (1H, each br, 1-H), 6.48–6.50 (2H, m, olefinic H); ^{13}C NMR[7] ($CDCl_3$) δ: 28.48 (q), 33.85 (d), 44.58 (d), 44.64 (d), 46.46 (d), 46.78 (t), 47.25 (t), 47.57 (d), 48.59 (d), 51.87 (q), 79.92 (s), 80.16 (s), 131.18 (d), 131.33 (d), 132.68 (d), 132.76 (d), 154.23 (s), 155.54 (s), 170.96 (s), 171.20 (s), 172.53 (s), 172.66 (s); IR (neat): 1746 (C═O), 1692 (C═O) cm^{-1}; HRMS calcd for $C_{16}H_{23}NO_6$ (M^+): 325.1525, found 325.1525.

2.1.8. 2-*tert*-Butyl 5,6-dimethyl (1*R,4*S**,5*S**,6*S**)-2-azabicyclo[2.2.2]oct-7-ene-2,5,6-tricarboxylate (9).** This compound (4.72 g, 82%) was obtained as colorless needles (hexane), mp 79–80°C, from **3** (5.00 g, 17.7 mmol) in a similar manner to that described for **8**. ^{1}H NMR[7] ($CDCl_3$) δ: 1.41 and 1.44 (9H, each s, $C(CH_3)_3$), 2.92–2.99 (2H, m, 3-Ha and 4-H), 3.21–3.26 (1H, m, 5-H), 3.34–3.39 (2H, m, 3-Hb and 6-H), 3.67 and 3.68 (3H, each s, OCH_3), 3.72 and 3.75 (3H, each s, OCH_3), 4.98 and 5.08 (1H, each d, *J*=5.7 Hz, 1-H), 6.34–6.38 and 6.47–6.53 (2H, m, olefinic H); ^{13}C NMR[7] ($CDCl_3$) δ: 28.35 (q), 28.43 (q), 33.20 (d), 33.30 (d), 42.40 (d), 42.70 (d), 46.31 (t), 46.49 (t), 47.59 (d), 48.19 (d), 48.36 (d), 48.69 (d), 52.23 (q), 52.28 (q), 52.47 (q), 79.60 (s), 132.73 (d), 132.86 (d), 132.89 (d), 133.04 (d), 154.11 (s) 154.75 (s), 172.24 (s), 172.78 (s), 173.42 (s); IR (KBr): 1740 (C═O), 1698 (C═O) cm^{-1}; MS *m/z*: 325 (M^+). Anal. calcd for $C_{16}H_{23}NO_6$: C, 59.07; H, 7.13; N, 4.31. Found: C, 58.85; H, 6.97; N, 4.33.

2.1.9. 2-*tert*-Butyl 6-methyl (1*R,4*R**,6*R**)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (10).** Under an argon atmosphere, trimethylsilyl iodide (640 mg, 3.20 mmol) was added to a solution of **4a** (120 mg, 0.533 mmol) in CCl_4 (1.5 ml) at 0°C and the mixture was stirred in the dark at room temperature for 4 d. After the reaction mixture was cooled in an ice bath, water was added (6 ml) and the mixture was vigorously stirred for 1 h. The aqueous layer was separated, washed with $CHCl_3$ (15 ml×10) and benzene (10 ml), and concentrated under reduced pressure, giving a yellowish brown oil. Thionyl chloride (320 mg, 2.69 mmol) was added dropwise to MeOH (5 ml) at −10°C, and the mixture was stirred at room temperature for 30 min. The yellowish brown oil obtained previously was dissolved in MeOH (3 ml), which was added to the $SOCl_2$–MeOH solution, and the whole was stirred for 2 d. The reaction mixture was concentrated under reduced pressure. MeOH (20 ml) was added to the residue and the solution was concentrated under reduced pressure; this operation was then repeated 3 times. After the residue was dissolved in $CHCl_3$ (7.5 ml), triethylamine (160 mg, 1.60 mmol) was added dropwise at 0°C, and then Boc_2O (350 mg, 1.60 mmol) was added. The mixture was stirred in the dark at room temperature for 3 d, and concentrated under reduced pressure. The residue was extracted with $CHCl_3$ (15 ml) and water (10 ml), and the organic layer was washed with water (10 ml×3), dried over

anhydrous Na_2SO_4, and concentrated under reduced pressure to give a yellowish brown oil. It was subjected to column chromatography on silica gel [hexane–Et_2O (4:1)] to give **10** (120 mg, 84%) as a white solid, which was recrystallized from hexane to give colorless prisms, mp 116–118°C. Compounds **4b** and **4c** were similarly treated to **4a**, giving **10** in 75 and 77% yields, respectively. ^{1}H NMR[7] ($CDCl_3$) δ: 1.45 and 1.48 (9H, s, C(CH_3)$_3$), 1.84–1.87 (2H, m, 5-H), 2.79 (1H, m, 4-H), 2.88–2.93 (1H, m, 3-Ha), 3.06–3.08 (1H, m, 6-H), 3.22 (1H, m, 3-Hb), 3.65 and 3.67 (3H, each s, OCH_3), 4.94 and 5.14 (1H, each s, 1-H), 6.33–6.36 and 6.41–6.43 (2H, m, olefinic H); ^{13}C NMR[7] ($CDCl_3$) δ: 26.09 (t), 26.28 (t), 28.32 (q), 28.52 (q), 28.72 (q), 30.34 (d), 30.57 (d), 30.86 (d), 43.84 (d), 44.08 (d), 45.92 (d), 46.08 (d), 47.01 (t), 47.16 (t), 47.36 (t), 51.84 79.51 (s), 79.71 (s), 130.43 (d), 130.83 (d), 135.05 (d), 135.31 (d), 154.37 (s), 154.72 (s), 173.33 (s); IR (KBr): 1736 (C═O), 1682 (C═O) cm^{-1}; MS *m/z*: 267 (M^+). Anal. calcd for $C_{14}H_{21}NO_4$: C, 62.87; H, 7.74; N, 5.32. Found: C, 62.89; H, 7.92; N, 5.24.

2.1.10. 2-*tert*-Butyl 6-methyl (1*R,4*R**,6*S**)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (11).** This compound (118 mg, 83%) was obtained as a colorless oil from **5a** (120 mg, 0.533 mmol) in a manner similar to that described for **10**. Compounds **5b** and **5c** were treated similarly to **5a**, giving **11** in 66 and 47% yields, respectively. ^{1}H NMR[7] ($CDCl_3$) δ:1.41–1.44 (9H, s, C(CH_3)$_3$), 1.48–1.59 (1H, m, 5-Ha), 2.08–2.13 (1H, m, 5-Hb), 2.51–2.57 (1H, m, 6-H), 2.73 and 2.79 (1H, each s, 4-H), 2.89–2.96 (1H, m, 3-Ha), 3.30–3.37 (1H, m, 3-Hb), 3.64 and 3.72 (3H, m, OCH_3), 4.89–4.91 and 4.99–5.00 (1H, each m, 1-H), 6.41–6.49 (2H, m, olefinic H); ^{13}C NMR[7] ($CDCl_3$) δ: 24.97 (t), 25.29 (t), 28.40 (q), 28.46 (q), 28.52 (q), 30.15 (d), 30.40 (d), 30.56 (d), 44.31 (d), 44.63 (d), 47.03 (t), 47.25 (t), 47.36 (t), 47.47 (t), 48.53 (d), 51.91 (q), 52.08 (q), 79.17 (s), 131.86 (d), 132.23 (d), 135.06 (d), 135.15 (d), 135.20 (d), 154.25 (s), 154.90 (s), 173.60 (s), 174.10 (s); IR (neat): 1738 (C═O), 1693 (C═O) cm^{-1}; HRMS calcd for $C_{14}H_{21}NO_4$ (M^+): 267.1471, found 267.1476.

2.1.11. 1-(*tert*-Butoxycarbonyl)-*c*-3,*c*-4-bis(methoxycarbonyl)-*r*-2,*c*-5-piperidinedicarboxylic acid (12). A solution of **8** (1.00 g, 3.07 mmol) in AcOEt (60 ml), $RuO_2{\cdot}xH_2O$ (10 mg), and a 10% $NaIO_4$ aqueous solution (36.2 ml) were mixed and then vigorously stirred at 0°C for 24 h. The AcOEt layer was separated, and the aqueous layer was extracted with AcOEt (50 ml×3). The resulting aqueous layer was concentrated to a half volume under reduced pressure, and extracted with AcOEt (60 ml×3). Isopropyl alcohol (1 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 residual gray oil was subjected to column chromatography on silica gel [AcOEt–MeOH (20:1)] to give a white solid. It was recrystallized from AcOEt–hexane to give **12** (1.08 g, 90%) as colorless needles, mp 175–176°C (dec.). ^{1}H NMR[7] [$(CD_3)_2CO$] δ: 1.45 (9H, s, C(CH_3)$_3$), 2.81 and 2.88 (1H, each br, 5-H), 3.41–3.45 (1H, m, 3-H), 3.60 (3H, s, OCH_3), 3.76–3.81 (5H, m, OCH_3, 4-H, and 6-Ha), 4.25 and 4.36 (1H, br, 6-Hb), 5.15 and 5.32 (1H, s, 2-H), 9.12 (2H, br, 2×OH); ^{13}C NMR[7] [$(CD_3)_2CO$] δ: 28.45 (q), 38.68 (t), 39.83 (t), 40.80 (d), 43.29 (d), 43.55 (d), 45.22 (d), 45.48 (d), 51.56 (q), 52.28 (q), 52.84 (d), 54.10 (d), 80.78 (s), 155.21 (s) 155.52 (s), 170.04 (s), 170.11 (s), 170.98 (s), 171.89 (s), 172.34 (s); IR (KBr): 3456 (OH, NH), 1740 (C═O), 1708 (C═O), 1654 (C═O), 1639 (C═O)cm^{-1}; MS (FAB) *m/z*: 390 (M^++1). Anal. calcd for $C_{16}H_{23}NO_{10}$: C, 49.36; H, 5.95; N, 3.60. Found: C, 49.23; H, 5.89; N, 3.58.

2.1.12. 1-(*tert*-Butoxycarbonyl)-*t*-3,*t*-4-bis(methoxycarbonyl)-*r*-2,*c*-5-piperidinedicarboxylic acid (13). A solution of **9** (3.00 g, 9.22 mmol) in AcOEt (180 ml), $RuO_2{\cdot}xH_2O$ (30 mg), and a 10% $NaIO_4$ aqueous solution (108.6 ml) were mixed and then vigorously stirred at 0°C for 24 h. The AcOEt layer was separated, and the aqueous layer was extracted with AcOEt (100 ml×3). The resulting aqueous layer was concentrated to a half volume under reduced pressure, and extracted with AcOEt (100 ml×3). Isopropyl alcohol (1 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 residual gray oil was subjected to column chromatography on silica gel [hexane–AcOEt (1:1)] to give a white solid. It was recrystallized from AcOEt–hexane to give **13** (3.02 g, 84%) as colorless prisms, mp 166–168°C (dec.). ^{1}H NMR[7] [$(CD_3)_2CO$] δ: 1.45 (9H, s, C(CH_3)$_3$), 2.81 and 2.88 (1H, each br, 5-H), 3.41–3.45 (1H, m, 3-H), 3.60 (3H, s, OCH_3), 3.76–3.81 (5H, m, OCH_3, 4-H, and 6-Ha), 4.25 and 4.36 (1H, br, 6-Hb), 5.41 (1H, br, 2-H), 8.39–11.77 (2H, br, 2×OH); ^{13}C NMR[7] [$(CD_3)_2CO$] δ: 28.39 (q), 38.86 (d), 39.86 (t), 40.06 (d), 40.32 (t), 43.63 (d), 52.20 (q), 53.19 (q), 53.90 (d), 54.84 (d), 80.62 (s), 155.16 (s) 155.84 (s), 171.13 (s), 172.01 (s), 172.04 (s), 172.45 (s), 172.72 (s); IR (KBr): 3450 (OH, NH), 1761 (C═O), 1741 (C═O), 1716 (C═O), 1701 (C═O), 1662 (C═O) cm^{-1}; MS (FAB) *m/z*: 390 (M^++1). Anal. calcd for $C_{16}H_{23}NO_{10}$: C, 49.36; H, 5.95; N, 3.60. Found: C, 49.41; H, 5.89; N, 3.56.

2.1.13. 1-(*tert*-Butoxycarbonyl)-*c*-3-(methoxycarbonyl)-*r*-2,*c*-5-piperidinedicarboxylic acid (14) and 1-*tert*-butyl 2,3,5-trimethyl 1,*r*-2,*c*-3,*c*-5-piperidinetetracarboxylate (14′). A solution of **10** (100 mg, 0.374 mmol) in AcOEt (5.4 ml), $RuO_2{\cdot}xH_2O$ (0.9 mg), and a 10% $NaIO_4$ aqueous solution (4.4 ml) were mixed and then vigorously stirred at 0°C for 96 h. The AcOEt layer was separated, and the aqueous layer was extracted with AcOEt (15 ml×3). The resulting aqueous layer was concentrated to a half volume under reduced pressure, and extracted with AcOEt (10 ml×3). Isopropyl alcohol (0.5 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 residual pale yellow oil was subjected to column chromatography on silica gel (AcOEt) to give **14** (120 mg, 97%) as an amorphous solid. For the analysis, a part of this solid (59 mg) was dissolved in MeOH (3 ml) and treated with diazomethane. The solution was concentrated, and the residual gray oil was subjected to column chromatography on silica gel (benzene, then $CHCl_3$) to give trimethyl ester **14′** (63.4 mg, 99%) as a colorless oil. ^{1}H NMR[7] ($CDCl_3$) δ: 1.49 (9H, s, C(CH_3)$_3$),

1.73–1.79 (1H, m, 4-Ha), 2.40–2.51 (2H, m, 4-Hb and 5-H), 2.60–2.95 (2H, m, 3-H and 6-Ha), 3.71 and 3.75 (9H, each s, 3×OCH_3), 4.20 and 4.37 (1H, each br, 6-Hb), 5.29 and 5.54 (1H, each s, 2-H); ^{13}C NMR[7] ($CDCl_3$) δ: 25.44 (t), 25.61 (t), 28.31 (q), 40.57 (d), 40.83 (d), 41.89 (t), 42.14 (d), 42.46 (d), 42.88 (t), 45.48 (d), 51.99 (q), 52.16 (q), 52.49 (q), 54.74 (d), 55.89 (d), 81.21 (s), 154.46 (s) 154.87 (s), 169.81 (s), 171.04 (s), 171.11 (s), 172.62 (s), 172.72 (s); IR (neat): 1736 (C═O), 1701 (C═O), 1693 (C═O) cm^{-1}; HRMS calcd for $C_{16}H_{25}NO_8$ (M^+): 359.1580, found 359.1582.

2.1.14. 1-(*tert*-Butoxycarbonyl)-*t*-3-(methoxycarbonyl)-*r*-2,*c*-5-piperidinedicarboxylic acid (15) and 1-*tert*-butyl 2,3,5-trimethyl 1,*r*-2,*t*-3,*c*-5-piperidinetetracarboxylate (15′). A solution of **11** (100 mg, 0.374 mmol) in AcOEt (5.4 ml), $RuO_2{\cdot}xH_2O$ (0.9 mg), and a 10% $NaIO_4$ aqueous solution (4.4 ml) were mixed and then vigorously stirred at 0°C for 72 h. The AcOEt layer was separated, and the aqueous layer was extracted with AcOEt (15 ml×3). The resulting aqueous layer was concentrated to a half volume under reduced pressure, and extracted with AcOEt (10 ml×3). Isopropyl alcohol (0.5 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 residual pale yellow oil was subjected to column chromatography on silica gel [hexane–AcOEt (1:1)] to give **15** (120 mg, 97%) as an amorphous solid. For the analysis, a part of this solid (61.2 mg) was dissolved in MeOH (3 ml) and treated with diazomethane. The solution was concentrated, and the residual gray oil was subjected to column chromatography on silica gel (benzene, then $CHCl_3$) to give trimethyl ester **15′** (66.0 mg, 99%) as a colorless oil. ^{1}H NMR[7] ($CDCl_3$) δ: 1.46 and 1.47 (9H, each s, $C(CH_3)_3$), 1.56–1.62 (1H, m, 4-Ha), 2.44–2.46 (1H, m, 4-Hb), 2.65–2.69 and 2.74–2.80 (1H, each m, 5-H), 2.74–2.80 and 2.90–2.97 (1H, each m, 6-Ha), 3.36–3.38 (1H, m, 3-H), 3.68–3.80 (9H, m, 3×OCH_3), 4.16–4.21 and 4.37–4.40 (1H, m, 6-Hb), 5.42 and 5.50 (1H, each s, 2-H); ^{13}C NMR[7] ($CDCl_3$) δ: 25.08 (t), 25.26 (t), 28.25 (q), 37.30 (d), 37.48 (d), 39.72 (d), 40.16 (d), 41.91 (t), 43.05 (t), 51.88 (q), 52.34 (q), 52.37 (q), 54.72 (q), 54.60 (d), 55.65 (d), 80.75 (s), 80.92 (s), 154.63 (s) 155.12 (s), 170.51 (s), 170.66 (s), 171.93 (s), 172.12 (s), 173.06 (s), 173.21 (s); IR (neat): 1738 (C═O), 1703 (C═O) cm^{-1}; HRMS calcd for $C_{16}H_{25}NO_8$ (M^+): 359.1580, found 359.1580.

2.1.15. *r*-2,*c*-3,*c*-4,*c*-5-Piperidinetetracarboxylic acid (16). A mixture of **12** (1.50 g, 3.85 mmol) and 6 M HCl (200 ml) was heated at 50°C for 3 weeks, and the solution was concentrated under reduced pressure. Water (100 ml) was added to the residue and the solution was concentrated under reduced pressure; this operation was then repeated 4 times to give **16**·HCl (1.15 g, 100%) as a pale yellow solid. It was dissolved in a minimum amount of water, and the pH of the solution was adjusted to 4 with 2 M NaOH, giving a precipitate, which was recrystallized from water to give **16** (900 mg, 89%) as colorless prisms, mp 211°C (dec.). ^{1}H NMR (2 M DCl) δ: 3.43 (1H, dd, J=13.6, 4.4 Hz, 6-Ha), 3.52 (2H, m, 4-H and 5-H), 3.92 (1H, dd, J=13.6, 2.2 Hz, 6-Hb), 3.94 (1H, d, J=3.7 Hz, 3-H), 4.43 (1H, d, J=3.7 Hz, 2-H); ^{13}C NMR (2 M DCl) δ: 34.08 (d), 36.94 (d), 38.31 (d), 40.59 (t), 53.69 (d), 165.40 (s), 169.79 (s), 169.93 (s), 170.03 (s); IR (KBr): 3086 (NH), 1734 (C═O), 1712 (C═O), 1579 (C═O) cm^{-1}; MS (FAB) m/z: 262 (M^++1). Anal. calcd for $C_9H_{11}NO_8$: C, 41.39; H, 4.24; N, 5.36. Found: C, 41.22; H, 4.20; N, 5.21.

2.1.16. *r*-2,*t*-3,*t*-4,*c*-5-Piperidinetetracarboxylic acid (17). A mixture of **13** (100 mg, 0.257 mmol) and 6 M HCl (15 ml) was heated at 50°C for 3 weeks, and the solution was concentrated under reduced pressure. Water (10 ml) was added to the residue and the solution was concentrated under reduced pressure; this operation was then repeated 4 times to give **17**·HCl (76 mg, 100%) as a white solid. It was dissolved in a minimum amount of water, and the pH of the solution was adjusted to 4 with 2 M NaOH, giving a precipitate, which was recrystallized from water to give **17**·H_2O (65 mg, 91%) as a white powder, mp 198°C (dec.). ^{1}H NMR (2 M DCl) δ: 3.42–3.45 (1H, m, 5-H), 3.54 (1H, dd, J=13.6, 4.9 Hz, 6-Ha), 3.58–3.60 (2H, m, 3-H and 4-H), 3.84 (1H, dd, J=13.6, 6.6 Hz, 6-Hb), 4.49 (1H, m, 2-H); ^{13}C NMR (2 M DCl) δ: 34.33 (d), 38.26 (d), 38.48 (d), 38.69 (t), 52.46 (d), 165.13 (s), 169.97 (s), 170.34 (s); IR (KBr): 3820–2350 (NH, OH), 1736 (C═O), 1728 (C═O), 1672 (C═O) cm^{-1}; MS (FAB) m/z: 262 (M^++1). Anal. calcd for $C_9H_{11}NO_8{\cdot}H_2O$: C, 38.72; H, 4.69; N, 5.02. Found: C, 38.75; H, 4.50; N, 5.04.

2.1.17. *r*-2,*c*-3,*c*-5-Piperidinetricarboxylic acid (18). A mixture of **14** (214 mg, 0.646 mmol) and 6 M HCl (37 ml) was heated at 50°C for 13 d, and the solution was concentrated under reduced pressure. Water (20 ml) was added to the residue and the solution was concentrated under reduced pressure; this operation was then repeated 4 times to give **18**·HCl (163 mg, 99%) as a pale yellow solid. It was dissolved in MeOH (1.2 ml) at 60°C, and propylene oxide (0.4 ml) was added to the solution with vigorous stirring. After cooling in an ice bath, the precipitate was filtered and recrystallized from water–EtOH, giving **18** (128 mg, 91%) as a white powder, mp 240°C (dec.). ^{1}H NMR (2 M DCl) δ: 2.35–2.39 (1H, m, 4-Ha), 2.52 (1H, m, 4-Hb), 3.10 (1H, m, 5-H), 3.34–3.37 (1H, m, 6-Ha), 3.52 (1H, d, J=2.6 Hz, 3-H), 3.76 (1H, d, J=12.5 Hz, 6-Hb), 4.40 (1H, d, J=2.6 Hz, 2-H); ^{13}C NMR (2 M DCl) δ: 25.18 (t), 35.60 (d), 38.94 (d), 44.42 (t), 56.76 (d), 169.58 (s), 175.42 (s), 175.26 (s); IR (KBr): 3170 (NH), 1716 (C═O), 1604 (C═O), 1571 (C═O) cm^{-1}; MS (FAB) m/z: 218 (M^++1). Anal. calcd for $C_8H_{11}NO_6$: C, 44.24; H, 6.45; N, 5.11. Found: C, 44.26; H, 6.25; N, 5.06.

2.1.18. *r*-2,*t*-3,*c*-5-Piperidinetricarboxylic acid (19). A mixture of **15** (102 mg, 0.308 mmol) and 6 M HCl (18 ml) was heated at 50°C for 13 d, and the solution was concentrated under reduced pressure. Water (10 ml) was added to the residue and the solution was concentrated under reduced pressure; this operation was then repeated 4 times to give **19**·HCl (78 mg, 100%) as a pale yellow solid. It was dissolved in a minimum amount of water, and the pH of the solution was adjusted to 4 with 2 M NaOH, giving a precipitate, which was recrystallized from water to give **19**·H_2O (65 mg, 90%) as a colorless prisms, mp 227°C (dec.). ^{1}H NMR (2 M DCl) δ: 2.20–2.31 (2H, m, 4-H), 3.05 (1H, m, 5-H), 3.31 (1H, ddd, J=7.3, 7.3, 4.8 Hz, 3-H), 3.45 (1H,

dd, J=13.3, 4.2 Hz, 6-Ha), 3.59 (1H, dd, J=13.3, 7.0 Hz, 6-Hb), 4.40 (1H, d, J=2.6 Hz, 2-H); ^{13}C NMR (2 M DCl) δ: 26.36 (t), 35.92 (d), 39.73 (d), 43.86 (t), 56.21 (d), 169.16 (s), 174.99 (s), 175.08 (s); IR (KBr): 3448 (OH, NH), 1732 (C=O), 1697 (C=O), 1628 (C=O) cm^{-1}; MS (FAB) m/z: 218 (M^++1). Anal. calcd for $C_9H_{11}NO_8 \cdot H_2O$: C, 40.85; H, 5.57; N, 5.96. Found: C, 40.90; H, 5.60; N, 6.00.

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6. The MOPAC AM1 method was performed on a personal computer using the program Chem 3D Pro (ver. 5.0); the coefficients (pz) of the HOMO of Moc-DHP were as follows: N(1), −0.4424, C(3), −0.4431, C(4), −0.2753, C(5), 0.4854, C(6), 0.3838. Those of the LUMO of methyl acrylate were as follows: O(1′), −0.3450, C(2′), 0.4259, C(3′), 0.4836, C(4′), −0.6601. The new bonds would form between C(3) and C(4′), and between C(6) and C(3′). As for the secondary orbital interaction, the sign of the coefficient at C(2′) coincides with that at C(5), but is opposed to that at N(1).
7. Some signals were split or broadened due to the rotamers or the conformers.