Stereospecific Synthesis of New 4-Amino-1,2,3-cyclohexanetricarboxylic Acids and 4-Amino-1,3-cyclohexanedicarboxylic Acids

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Diels–Alder adducts of 1,2-dihydropyridine with maleic and acrylic acid derivatives were stereospecifically converted by way of RuO_4 oxidation into new 4-amino-1,2,3-cyclohexanetricarboxylic acids and 4-amino-1,3-cyclohexanedicarboxylic acids.

Key words 1,2-dihydropyridine; Diels–Alder adduct; ruthenium tetroxide; 4-amino-1,2,3-cyclohexanetricarboxylic acid; 4-amino-1,3-cyclohexanedicarboxylic acid

We recently reported the stereospecific synthesis of 2,3,4,5-piperidinetetracarboxylic acids and 2,3,5-piperidinetricarboxylic acids with a *cis*-2,5-dicarboxy configuration from *N*-methoxycarbonyl-1,2-dihydropyridine (**1**), as a study of the synthesis of amino acids using Diels–Alder (D–A) adducts of dienophiles and *N*-containing dienes.[1)] The intermediate products, isoquinuclidines **2**—**7**,[1)] seemed to be convertible to other amino acids. In the present paper, we would like to report the synthesis of new 4-amino-1,2,3-cyclohexanetricarboxylic acids and 4-amino-1,3-cyclohexanedicarboxylic acids with a 1,4-*cis*-configuration. Aminocyclohexanecarboxylic acid derivatives have been examined for bioactive compounds such as the inhibitor of the γ-aminobutyric acid (GABA) receptor.[2)] Although ethyl esters of 4-amino-1,3-cyclohexanedicarboxylic acids were synthesized by Škarić *et al.*,[3)] free amino acids have not yet been synthesized and isolated.

First, D–A adducts **2**—**7** were hydrogenated in the presence of 10% Pd/C under ordinary pressure to give compounds **8**—**13** (Fig. 2) quantitatively, respectively. Although no effective data regarding the stereochemistry of compound **3** in comparison with that of compound **2** were obtained by a nuclear Overhauser effect (NOE) experiment in the ^{1}H-NMR analysis, in the analysis of **9**, +NOEs were observed between H^5 and H^{8b} between H^6 and H^{7b}, and −NOE was observed between H^6 and H^{7a} (Fig. 3). Therefore, the stereochemistry of **3** simultaneously became clear.

Next, as removal of the *N*-methoxycarbonyl (Moc) group seemed to be difficult in the later steps, Moc groups of **8**—**13** were converted into *tert*-butoxycarbonyl (Boc) groups (Chart 1). Compounds **8**—**11** were treated with trimethylsilyl iodide[4—8)] in CCl_4 followed by treatments with water, respectively, to cause removal of the *N*-Moc groups as well as dealkylation and hydrolysis of the ester groups. Thus obtained hydroiodides of amino acids were esterified with $SOCl_2$–MeOH, and introductions of a Boc group were achieved by treatments with Boc_2O in $CHCl_3$, giving **14**—**17** in 87, 90, 84, and 85% yields, respectively. In the case of **12** and **13**, as these carboxylic acids were sparingly soluble in CCl_4, $CHCl_3$ was used as a solvent for removal of the Moc group. Similar treatments of the corresponding amino acids gave **16** and **17** in 85% yields, respectively. No epimerization was observed in the above cases, although when **10** and **11** were similarly treated with trimethylsilyl iodide in $CHCl_3$, the epimerizations occurred and the resultant products became mixtures of **16** and **17**, respectively.

Conversion of the methylene groups adjacent to *N*-atoms into carbonyl groups was achieved by ruthenium tetroxide (RuO_4) oxidation.[9—13)] Under similar conditions employing AcOEt as a reaction solvent, compounds **14**—**17** disappeared after 2, 3.5, 1.5, and 3 h and gave lactams **18**—**21** in 92, 95, 96, and 97% yields, respectively. Although the yields of the resultant lactams were almost quantitative, the longer reaction times were required when the ester groups were situated near to the methylene groups that would be oxidized. The reaction rates of the oxidations seemed to be influenced by the steric hindrances of the ester groups, and/or by the electrostatic repulsions between the ester groups and RuO_4.

Finally, hydrolyses of lactams **18**—**21** were attempted. Treatments of **18** and **19** with 6 M HCl–AcOH at 50 °C for

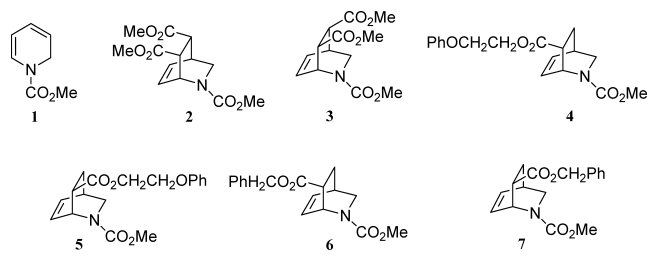

Fig. 1

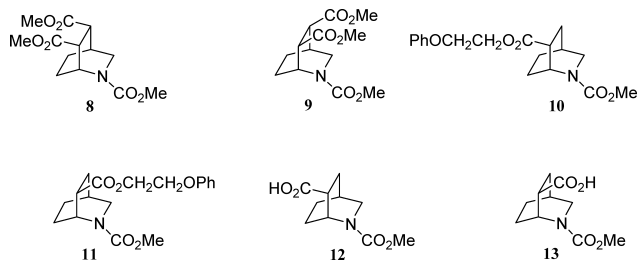

Fig. 2

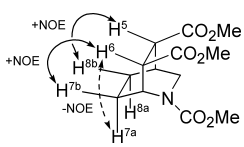

Fig. 3. Selected Decisive NOE Relationships of Compound **9**

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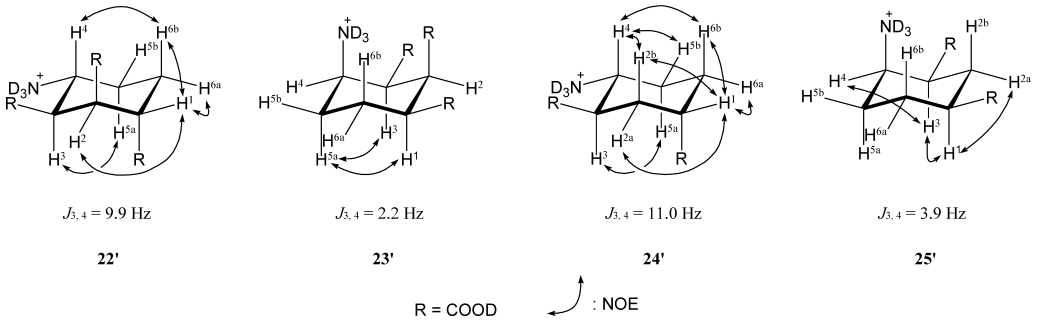


Fig. 4. Selected Decisive Coupling Constants and NOE Relationships of the Target Amino Acids **22**, **23**, **24**, and **25** in 2 M DCl (**22′**, **23′**, **24′**, **25′**)

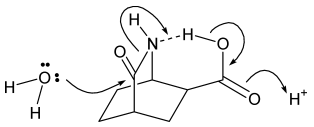
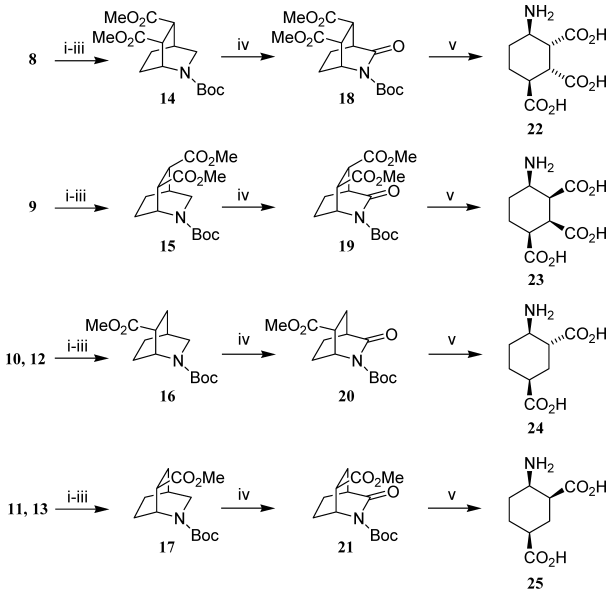


Fig. 5. The Acceleration Effect by the Carboxy Group in the Hydrolysis of Compound **21**

21 d quantitatively gave the expected hydrochlorides of amino acids **22** and **23**, respectively. These hydrochlorides were dissolved in small amounts of water and the solutions were adjusted to pH 4 with 2 M NaOH, giving free amino acids **22** and **23** as crystals in 86 and 84% yields, respectively. When the hydrolyses of **18** and **19** were executed at 100 °C, the reaction intermediates, which were observed by monitoring with ^{1}H-NMR spectra in the cases of the hydrolyses at 50 °C, disappeared within 7 d, but the NMR analysis showed that the expected amino acids seemed to be contaminated with considerable amounts of the stereoisomers.

The stereochemistries of compounds **22** and **23** were confirmed by NMR spectroscopy (NOE analysis after assignment of the signals with H–H COSY and C–H COSY spectra) as shown in Fig. 4. In the case of **22**, as the coupling constant between H^3 and H^4 was 9.9 Hz and NOEs were observed between H^3 and H^{5a} and between H^4 and H^{6b}, the relative configuration of H^3 and H^4 proved to be *trans-diaxial*. As an NOE was observed between H^1 and H^{6b}, the relative configuration of H^1 and H^4 proved to be *cis*. As an NOE was observed between H^2 and H^3 and no NOE was observed between H^2 and H^4, the relative configuration of H^2 and H^3 proved to be *cis*. These data support our hypothesis that **22** is *c*-4-amino-*r*-1,*t*-2,*t*-3-cyclohexanetricarboxylic acid. In the case of **23**, as the coupling constant between H^3 and H^4 was 2.2 Hz, the relative configuration of H^3 and H^4 proved to be *cis*. As NOEs were observed between H^1 and H^{5a} and between H^3 and H^{5a} and no NOE was observed between H^2 and H^{6b}, the relative configurations between H^1, H^2 and H^3 proved to be all *cis*. Thus compound **23** was identified as *c*-4-amino-*r*-1,*c*-2,*c*-3-cyclohexanetricarboxylic acid.

Hydrolysis of **20** with 6 M HCl–AcOH at 50 °C was completed in 14 d and that of **21** under similar conditions was completed in 7 d, producing the expected hydrochlorides of amino acids **24** and **25** quantitatively, respectively. These hydrochlorides were also dissolved in small amounts of water, and the solutions were adjusted to pH 4 with 2 M NaOH, giving free amino acids **22** and **23** as crystals in 85 and 82% yields, respectively. When **20** and **21** were treated with 1 M HCl–AcOH at 50 °C for 1 d, respectively, the ^{1}H-NMR analysis of the reaction intermediates showed the complete removal of Boc groups and the complete hydrolysis of methyl ester groups. These results imply that hydrolysis of the lactam group in this reaction is the rate-determining step. We therefore believe that the faster rate of hydrolysis of **21** can be attributed to the acceleration by the carboxy group, as shown in Fig. 5.



Reagents and conditions: i, Me_3SiI, CCl_4 or $CHCl_3$, 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, room temp; v, 6M HCl, 50°C.

Chart 1. Conversion of D–A Adducts into the Amino Acids

The stereochemistries of **24** and **25** were analyzed similarly to **22** and **23**. In the case of **24**, as the coupling constant between H^3 and H^4 was 11.0 Hz and NOEs were observed between H^3 and H^{5a}, between H^{2b} and H^4, and between H^4 and H^{6b}, the relative configuration of H^3 and H^4 proved to be *trans-diaxial*. As NOEs were also observed between H^1 and H^{2b} and between H^1 and H^{6b}, the relative configuration of H^1 and H^4 proved to be *cis*. Thus compound **24** was identified as *c*-4-amino-*r*-1,*t*-3-cyclohexanedicarboxylic acid. In the case of **25**, as the coupling constant between H^3 and H^4 was 3.9 Hz, the relative configuration of H^3 and H^4 proved to be *cis*. As NOEs were observed between H^1, H^{2a}, and H^3, the relative configuration between H^1 and H^3 proved to be *cis*. Thus compound **25** was identified as *c*-4-amino-*r*-1,*c*-3-cy-

clohexanedicarboxylic acid.

In conclusion, we succeeded in stereospecifically synthesizing new 4-amino-1,2,3-cyclohexanetricarboxylic acids **22** and **23** as well as 4-amino-1,3-cyclohexanedicarboxylic acids **24** and **25** from Diels–Alder adducts.

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. NMR spectra, except for the amino acids, were recorded in chloroform-*d* ($CDCl_3$) on a JEOL GSX-400 spectrometer 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). NOE spectra were measured in the differential modes. Infrared (IR) spectra were recorded on a Hitachi 270-30 spectrophotometer. Mass spectra (MS) were obtained with a JEOL JMS-DX300 instrument. Column chromatography was performed on silica gel (Kieselgel 60, 70—230 mesh, Merck).

Trimethyl (1*R,4*S**,5*R**,6*R**)-2-Azabicyclo[2.2.2]octane-2,5,6-tricarboxylate (8)** Compound **2** (870 mg, 3.07 mmol) was hydrogenated in MeOH (9 ml) in the presence of 10% Pd/C (87 mg) under atmospheric pressure for 1 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give **8** (873 mg, 100%) as a white solid. It was recrystallized from *i*-Pr_2O to give colorless prisms, mp 78.5—79 °C. ^{1}H-NMR[14] ($CDCl_3$) δ: 1.50—1.55 (1H, m, 8-Ha), 1.75—1.82 (1H, m, 7-Ha), 1.88—1.97 (2H, m, 7-Hb, 8-Hb), 2.33 and 2.38 (1H, m, J=4.8, 2.4 Hz, 4-H), 3.00—3.07 (1H, m, 5-H), 3.17—3.20 and 3.25—3.28 (1H, m, 6-H), 3.39—3.44 (2H, m, 3-H), 3.65 and 3.67 (6H, each s, 2×OCH_3), 3.72 (3H, m, $NCOOCH_3$), 4.30 and 4.33 (1H, each dd, J=4.0, 2.0 Hz, 1-H). ^{13}C-NMR[14] ($CDCl_3$) δ: 20.04 (t), 20.13 (t), 22.73 (t), 28.77 (d), 28.86 (d), 42.91 (d), 44.94 (d), 45.25 (d), 45.63 (d), 49.11 (t), 49.19 (t), 51.80 (q), 52.48 (q), 52.54 (q), 155.59 (s), 155.63 (s), 171.71 (s), 172.84 (s). IR ν_{max}^{KBr} cm^{-1}: 1747 (C=O), 1698 (C=O). MS *m/z*: 285 (M^+). *Anal.* Calcd for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.88; H, 6.61; N, 4.93.

Trimethyl (1*R,4*S**,5*S**,6*S**)-2-Azabicyclo[2.2.2]octane-2,5,6-tricarboxylate (9)** Compound **3** (870 mg, 3.07 mmol) was hydrogenated in MeOH (9 ml) in the presence of 10% Pd/C (87 mg) under atmospheric pressure for 1 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give **9** (872 mg, 100%) as a white solid. It was recrystallized from *i*-Pr_2O to give colorless needles, mp 97—98 °C. ^{1}H-NMR[14] ($CDCl_3$) δ: 1.54—1.60 (2H, m, 8-H), 1.70—1.79 (1H, m, 7-Hb), 1.84—1.95 (1H, m, 7-Ha), 2.41 and 2.46 (1H, each dd, J=5.6, 2.8 Hz, 4-H), 3.20—3.25 (1H, m, 6-H), 3.30—3.35 (2H, m, 3-Ha, 5-H), 3.46—3.49 (1H, m, 3-Hb), 3.67, 3.70, 3.71 and 3.73 (9H, each s, 3×OCH_3), 4.41 and 4.52 (1H, each dd, J=4.0, 2.0 Hz, 1-H). ^{13}C-NMR[14] ($CDCl_3$) δ: 19.85 (t), 19.92 (t), 22.06 (t), 26.27 (t), 28.93 (d), 28.97 (d), 42.78 (d), 42.83 (d), 45.63 (d), 45.71 (d), 46.23 (d), 46.71 (d), 48.69 (t), 52.24 (q), 52.31 (q), 52.46 (q), 155.76 (s), 155.95 (s), 173.04 (s), 173.51 (s), 173.84 (s), 173.88 (s). IR ν_{max}^{KBr} cm^{-1}: 1733 (C=O), 1693 (C=O). MS *m/z*: 285 (M^+). *Anal.* Calcd for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.63; H, 6.82; N, 4.90.

2-Methyl 6-(2-Phenoxyethyl) (1*R,4*S**,6*R**)-2-Azabicyclo[2.2.2]octane-2,6-dicarboxylate (10)** Compound **4** (2.23 g, 6.37 mmol) was hydrogenated in MeOH (22 ml) in the presence of 10% Pd/C (223 mg) under atmospheric pressure for 1 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give **10** (2.25 g, 100%) as a colorless oil. ^{1}H-NMR[14] ($CDCl_3$) δ: 1.55—1.58 (1H, m, 8-Ha), 1.70—1.81 (4H, m, 5-Ha, 7-H, 8-Hb), 1.93—1.97 (1H, m, 4-H), 2.11—2.14 (1H, m, 5-Hb), 2.92—2.99 (1H, m, 6-H), 3.23—3.33 (2H, m, 3-H), 3.68 (3H, m, OCH_3), 4.14—4.18 and 4.39—4.50 (5H, m, 1-H and $-CH_2CH_2-$), 6.88—6.97 and 7.25—7.30 (5H, m, aromatic H). ^{13}C-NMR[14] ($CDCl_3$) δ: 22.94 (t), 23.13 (t), 23.60 (t), 23.67 (t), 25.60 (d), 25.78 (d), 26.64 (t), 42.76 (d), 42.91 (d), 45.16 (d), 45.68 (d), 48.59 (t), 48.62 (t), 52.35 (q), 63.01 (t), 63.12 (t), 65.66 (t), 65.78 (t), 114.63 (d), 121.16 (d), 121.26 (d), 129.49 (d), 129.53 (d), 155.64 (s), 155.79 (s), 158.40 (s), 158.43 (s), 173.30 (s), 173.38 (s). IR ν_{max}^{KBr} cm^{-1}: 1735 (C=O), 1693 (C=O). HR-MS *m/z*: Calcd for $C_{18}H_{23}NO_5$: 333.1576 (M^+). Found: 333.1574.

2-Methyl 6-(2-Phenoxyethyl) (1*R,4*S**,6*S**)-2-Azabicyclo[2.2.2]octane-2,6-dicarboxylate (11)** Compound **5** (3.68 g, 11.1 mmol) was hydrogenated in MeOH (37 ml) in the presence of 10% Pd/C (368 mg) under atmospheric pressure for 1 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give **11** (3.69 g, 100%) as a colorless oil. ^{1}H-NMR[14] ($CDCl_3$) δ: 1.57—1.63 (2H, m, 8-H), 1.68—1.74 (2H, m, 5-Ha, 7-Ha), 1.91—2.00 (2H, m, 4-H, 7-Hb), 2.14—2.17 (1H, m, 5-Hb), 2.65—2.80 (1H, m, 6-H), 3.26—3.31 (1H, m, 3-Ha), 3.40—3.43 (1H, m, 3-Hb), 3.57 and 3.62 (3H, each s, OCH_3), 4.11—4.20 and 4.39—4.44 (5H, m, 1-H and $-CH_2CH_2-$), 6.90—6.97 and 7.26—7.30 (5H, m, aromatic H). ^{13}C-NMR[14] ($CDCl_3$) δ: 23.37 (t), 23.48 (t), 25.26 (d), 25.38 (d), 26.52 (t), 26.75 (t), 43.28 (d), 43.32 (d), 46.00 (d), 46.50 (d), 48.89 (t), 52.25 (q), 63.14 (t), 65.75 (t), 65.84 (t), 114.63 (d), 114.69 (d), 121.02 (d), 121.18 (d), 129.46 (d), 129.53 (d), 155.91 (s), 156.18 (s), 158.52 (s), 158.56 (s), 173.80 (s), 174.17 (s). IR ν_{max}^{KBr} cm^{-1}: 1735 (C=O), 1697 (C=O). HR-MS *m/z*: Calcd for $C_{18}H_{23}NO_5$: 333.1576 (M^+). Found: 333.1575.

(1*R,4*S**,6*R**)-2-Methoxycarbonyl-2-azabicyclo[2.2.2]octane-6-carboxylic Acid (12)** Compound **6** (8.25 g, 27.4 mmol) was hydrogenated in MeOH (83 ml) in the presence of 10% Pd/C (825 mg) under atmospheric pressure for 1.5 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give **12** (5.84 g, 100%) as a white solid. It was recrystallized from *i*-Pr_2O to give a white powder, mp 114—115 °C. ^{1}H-NMR[14] ($CDCl_3$) δ: 1.58—1.68 (2H, m, 8-H), 1.75—1.87 (3H, m, 5-Ha, 7-H), 1.97—2.04 (1H, m, 4-H), 2.08—2.14 (1H, m, 5-Hb), 2.96—3.02 (1H, m, 6-H), 3.35—3.40 (2H, m, 3-H), 3.73 (3H, m, OCH_3), 4.33 and 4.46 (1H, each dd, J=5.7, 3.2 Hz, 1-H), 10.00 (1H, br s, COOH). ^{13}C-NMR[14] ($CDCl_3$) δ: 22.94 (t), 23.12 (t), 23.66 (t), 23.72 (t), 25.59 (d), 25.75 (d), 26.46 (t), 26.53 (t), 42.71 (d), 42.85 (d), 45.17 (d), 45.69 (d), 48.61 (t), 52.60 (q), 52.66 (q), 155.90 (s), 156.08 (s), 177.99 (s), 178.16 (s). IR ν_{max}^{KBr} cm^{-1}: 3150 (OH), 1739 (C=O), 1654 (C=O). MS *m/z*: 213 (M^+). *Anal.* Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.30; H, 6.93; N, 6.55.

(1*R,4*S**,6*S**)-2-Methoxycarbonyl-2-azabicyclo[2.2.2]octane-6-carboxylic Acid (13)** Compound **7** (1.07 g, 3.55 mmol) was hydrogenated in MeOH (11 ml) in the presence of 10% Pd/C (107 mg) under atmospheric pressure for 1.5 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give **13** (755 mg, 100%) as a white solid. It was recrystallized from *i*-Pr_2O to give a white powder, mp 111—112 °C. ^{1}H-NMR[14] ($CDCl_3$) δ: 1.57—1.67 (2H, m, 8-H), 1.72—1.80 (2H, m, 5-Ha, 7-Ha), 1.89—2.03 (2H, m, 4-H, 7-Hb), 2.12—2.15 (1H, m, 5-Hb), 2.69—2.76 (1H, m, 6-H), 3.25—3.35 (1H, m, 3-Ha), 3.41—3.43 (1H, m, 3-Hb), 3.65 and 3.70 (3H, each s, OCH_3), 4.36 and 4.50 (1H, each br s, 1-H) 10.16 (1H, br s, COOH). ^{13}C-NMR[14] ($CDCl_3$) δ: 23.31 (t), 23.38 (t), 25.26 (d), 25.34 (d), 26.55 (t), 26.61 (t), 26.72 (t), 42.97 (d), 43.13 (d), 43.25 (d), 46.06 (d), 46.41 (d), 48.92 (t), 48.97 (t), 52.43 (q), 52.73 (q), 156.40 (s), 156.81 (s), 177.10 (s), 178.66 (s). IR ν_{max}^{KBr} cm^{-1}: 3160 (OH), 1745 (C=O), 1671 (C=O). MS *m/z*: 213 (M^+). *Anal.* Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.48; H, 7.03; N, 6.55.

2-*tert*-Butyl 5,6-Dimethyl (1*R,4*S**,5*R**,6*R**)-2-Azabicyclo[2.2.2]octane-2,5,6-tricarboxylate (14)** Under an argon atmosphere, trimethylsilyl iodide (10.6 g, 53.0 mmol) was added to a solution of **8** (4.68 g, 16.4 mmol) in CCl_4 (170 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 (8.20 g, 68.9 mmol) was added dropwise to MeOH (300 ml) at −10 °C, and the mixture was stirred at room temperature for 10 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 three 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 (6.00 g, 27.5 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. The oil was subjected to column chromatography on silica gel [hexane–AcOEt (8 : 1)] to give **14** (4.68 g, 87%) as a colorless oil. ^{1}H-NMR[14] ($CDCl_3$) δ: 1.47 (s, 9H, $C(CH_3)_3$), 1.52—1.55 (1H, m, 8-Ha), 1.70—1.80 (1H, m, 7-Ha), 1.85—1.95 (2H, m, 7-Hb, 8-Hb), 2.31 and 2.35 (1H, each dd, J=5.2, 2.4 Hz, 4-H), 2.97—3.06 (1H, m, 5-H), 3.15—3.20 and 3.25—3.28 (1H, m, 6-H), 3.36—3.40 (2H, m, 3-H), 3.66 and 3.68 (6H, each s, 2×OCH_3), 4.24 and 4.40 (1H, each dd, J=4.0, 2.0 Hz, 1-H). ^{13}C-NMR[14] ($CDCl_3$) δ: 20.07 (t), 20.16 (t), 22.75 (t), 22.84 (t), 28.53 (q), 28.88 (d), 29.06 (d), 42.94 (d), 43.03 (d), 44.62 (d), 44.92 (d), 45.07 (d), 45.76 (d), 48.68 (t), 49.54 (t), 51.73 (q), 51.76 (q), 79.68 (s), 79.88 (s), 154.53 (s), 171.87 (s), 172.97 (s). IR ν_{max}^{KBr} cm^{-1}: 1747 (C=O), 1693 (C=O). HR-MS

m/z: Calcd for $C_{16}H_{25}NO_6$: 327.1682 (M^+). Found: 327.1684.

2-*tert*-Butyl 5,6-Dimethyl (1*R,4*S**,5*S**,6*S**)-2-Azabicyclo[2.2.2]octane-2,5,6-tricarboxylate (15)** This compound (2.42 g, 90%) was obtained as a colorless oil from **9** (2.34 g, 8.20 mmol) in a manner similar to that described for **14**. ^{1}H-NMR[14] ($CDCl_3$) δ: 1.43 (9H, s, $C(CH_3)_3$), 1.54—1.58 (2H, m, 8-H), 1.69—1.77 (1H, m, 7-Ha), 1.84—1.90 (1H, m, 7-Hb), 2.38 and 2.45 (1H, each dd, J=5.6, 2.8 Hz, 4-H), 3.16—3.36 (3H, m, 3-Ha, 5-, 6-H), 3.42—3.47 (1H, m, 3-Hb), 3.69, 3.72, and 3.73 (9H, each s, 3×OCH_3), 4.34 and 4.48 (1H, each m, 1-H). ^{13}C-NMR[14] ($CDCl_3$) δ: 19.91 (t), 20.01 (t), 25.98 (t), 26.53 (t), 28.39 (q), 28.45 (q), 29.07 (d), 29.13 (d), 42.72 (d), 42.90 (d), 45.64 (d), 45.80 (d), 45.87 (d), 46.78 (d), 48.18 (t), 48.95 (t), 52.22 (q), 52.27 (q), 52.37 (q), 79.43 (s), 154.39 (s), 154.81 (s), 173.13 (s), 173.70 (s), 174.00 (s), 174.06 (s). IR ν_{max}^{KBr} cm^{-1}: 1736 (C=O), 1697 (C=O). HR-MS *m/z*: Calcd for $C_{16}H_{25}NO_6$: 327.1682 (M^+). Found: 327.1683.

2-*tert*-Butyl 6-Methyl (1*R,4*S**,6*R**)-2-Azabicyclo[2.2.2]octane-2,6-dicarboxylate (16)** From **10**: Under an argon atmosphere, trimethylsilyl iodide (7.07 g, 35.3 mmol) was added to a solution of **10** (5.47 g, 16.4 mmol) in CCl_4 (170 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 (8.20 g, 68.9 mmol) was added dropwise to MeOH (300 ml) at −10 °C, and the mixture was stirred at room temperature for 10 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 three 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 (6.00 g, 27.5 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. The oil was subjected to column chromatography on silica gel [hexane–AcOEt (8 : 1)] to give a white solid. It was recrystallized from *i*-Pr_2O, giving **16** (3.71 g, 84%) as colorless needles, mp 74.5—75.5 °C.

From **12**: Compound **12** (3.50 g, 16.4 mmol) was treated in a manner similar to the conversion of **10** into **16**, except that $CHCl_3$ was used as a reaction solvent of the first step instead of CCl_4, giving **16** (3.75 g, 85%). ^{1}H-NMR[14] ($CDCl_3$) δ: 1.47 (9H, s, $C(CH_3)_3$), 1.54—1.68 (3H, m, 7-Ha, 8-H), 1.72—1.84 (2H, m, 5-Ha, 7-Hb), 1.93—2.01 (1H, m, 4-H), 2.07—2.15 (1H, m, 5-Hb), 2.88—2.97 (1H, m, 6-H), 3.28—3.34 (2H, m, 3-H), 3.71 (3H, m, OCH_3), 4.19—4.22 and 4.36—4.39 (1H, each m, 1-H). ^{13}C-NMR[14] ($CDCl_3$) δ: 23.11 (t), 23.23 (t), 23.76 (t), 23.86 (t), 25.82 (d), 26.01 (d), 26.66 (t), 26.78 (t), 28.55 (q), 42.90 (d), 42.92 (d), 44.46 (d), 45.88 (d), 48.20 (t), 48.94 (t), 51.85 (q), 51.97 (q), 79.32 (s), 79.50 (s), 154.68 (s), 154.74 (s), 174.06 (s), 174.12 (s). IR ν_{max}^{KBr} cm^{-1}: 1735 (C=O), 1689 (C=O). MS *m/z*: 269 (M^+). *Anal.* Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.51; H, 8.33; N, 5.22.

2-*tert*-Butyl 6-Methyl (1*R,4*S**,6*S**)-2-Azabicyclo[2.2.2]octane-2,6-dicarboxylate (17)** From **11**: Compound **11** (5.47 g, 16.4 mmol) was treated in a manner similar to the conversion of **10** into **16** without recrystallization, giving **17** (3.76 g, 85%) as a colorless oil.

From **13**: Compound **13** (1.75 g, 8.21 mmol) was treated in a manner similar to the conversion of **10** into **16** without recrystallization, except that $CHCl_3$ was used as a reaction solvent of the first step instead of CCl_4, giving **17** (1.88 g, 85%). ^{1}H-NMR[14] ($CDCl_3$) δ: 1.43 (9H, s, $C(CH_3)_3$), 1.52—1.77 (4H, m, 5-Ha, 7-Ha, 8-H), 1.85—2.02 (2H, m, 5-Ha, 7-Ha), 2.10—2.20 (1H, m, 5-Hb), 2.62—2.73 (1H, m, 6-H), 3.18—3.28 (1H, m, 3-Ha), 3.33—3.43 (1H, m, 3-Hb), 3.57 and 3.62 (3H, each s, OCH_3), 4.27—4.30 and 4.35—4.38 (1H, m, 1-H). ^{13}C-NMR[14] ($CDCl_3$) δ: 23.45 (t), 23.66 (t), 25.34 (d), 25.55 (d), 26.51 (t), 26.53 (t), 26.62 (t), 27.01 (t), 43.43 (d), 43.47 (d), 45.36 (d), 46.61 (d), 48.40 (t), 49.20 (t), 51.87 (q), 52.02 (q), 79.00 (s), 79.02 (s), 154.60 (s), 155.05 (s), 174.38 (s), 174.87 (s). IR ν_{max}^{KBr} cm^{-1}: 1735 (C=O), 1693 (C=O). HRMS *m/z*: Calcd for $C_{14}H_{23}NO_4$: 269.1627 (M^+). Found: 269.1624.

2-*tert*-Butyl 5,6-Dimethyl (1*R,4*S**,5*R**,6*R**)-3-Oxo-2-azabicyclo[2.2.2]octane-2,5,6-tricarboxylate (18)** A solution of **14** (4.66 g, 14.2 mmol) in AcOEt (48 ml), $RuO_2 \cdot xH_2O$ (142 mg), and a 10% $NaIO_4$ aqueous solution (142 ml) were mixed and then vigorously stirred at room temperature for 2 h. The AcOEt layer was separated, and the aqueous layer was extracted with AcOEt (25 ml×3). Isopropyl alcohol (1 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 residual solid was recrystallized from *i*-Pr_2O to give **18** (4.49 g, 92%) as colorless needles, mp 130—132 °C. ^{1}H-NMR[14] ($CDCl_3$) δ: 1.53 (s, 9H, $C(CH_3)_3$), 1.76—1.81 (2H, m, 7-Ha, 8-Ha), 1.70—1.80 (1H, m, 7-Ha), 2.03—2.19 (2H, m, 7-Hb, 8-Hb), 2.93 (1H, m, 4-H), 3.15 (1H, ddd, J=11.3, 2.9, 1.5 Hz, 5-H), 3.32 (1H, ddd, J=11.3, 3.3, 1.1 Hz, 6-H), 3.69 and 3.70 (6H, each s, 2×OCH_3), 4.90 (1H, dd, m, 1-H). ^{13}C-NMR[14] ($CDCl_3$) δ: 18.43 (t), 21.57 (t), 27.92 (q), 27.99 (q), 28.02 (q), 28.13 (q), 40.25 (d), 42.47 (d), 44.73 (d), 51.29 (d), 51.35 (d), 51.40 (d), 51.84 (q), 51.94 (q), 51.97 (q), 52.03 (q), 52.13 (q), 52.18 (q), 52.24 (q), 52.32 (q), 83.82 (s), 149.92 (s), 170.76 (s), 171.14 (s), 171.99 (s). IR ν_{max}^{KBr} cm^{-1}: 1741 (C=O), 1733 (C=O), 1710 (C=O). MS *m/z*: 341 (M^+). *Anal.* Calcd for $C_{16}H_{23}NO_7$: C, 56.30; H, 4.10; N, 6.79. Found: C, 56.29; H, 4.07; N, 6.60.

2-*tert*-Butyl 5,6-Dimethyl (1*R,4*S**,5*S**,6*S**)-3-Oxo-2-azabicyclo[2.2.2]octane-2,5,6-tricarboxylate (19)** A solution of **15** (2.33 g, 7.12 mmol) in AcOEt (24 ml), $RuO_2 \cdot xH_2O$ (71 mg), and a 10% $NaIO_4$ aqueous solution (71 ml) were mixed and then vigorously stirred at room temperature for 3.5 h. The AcOEt layer was separated, and the aqueous layer was extracted with AcOEt (13 ml×3). Isopropyl alcohol (0.5 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 residual oil was subjected to column chromatography on silica gel (AcOEt), giving **19** (2.31 g, 95%) as a colorless oil. ^{1}H-NMR[14] ($CDCl_3$) δ: 1.52 (s, 9H, $C(CH_3)_3$), 1.67—1.91 (4H, m, 7-H, 8-H), 3.05 (1H, dd, J=5.1, 2.6 Hz, 4-H), 3.29 (1H, dd, J=5.5, 1.8 Hz, 5-H), 3.50 (1H, m, 6-H), 3.71 and 3.76 (6H, each s, 2×OCH_3), 5.05 (1H, dd, J=3.3, 1.5 Hz, 1-H). ^{13}C-NMR[14] ($CDCl_3$) δ: 18.43 (t), 21.56 (t), 27.78 (q), 27.96 (q), 41.71 (d), 42.30 (d), 44.91 (d), 52.34 (q), 52.37 (q), 52.51 (q), 52.56 (q), 52.76 (q), 83.46 (s), 150.10 (s), 171.26 (s), 171.98 (s), 172.17 (s). IR ν_{max}^{KBr} cm^{-1}: 1747 (C=O), 1714 (C=O). HR-MS *m/z*: Calcd for $C_{16}H_{23}NO_7$: 341.1475 (M^+). Found: 341.1477.

2-*tert*-Butyl 6-Methyl (1*R,4*S**,6*R**)-3-Oxo-2-azabicyclo[2.2.2]octane-2,6-dicarboxylate (20)** This compound (3.86 g, 96%) was obtained as colorless prisms, mp 79—80.5 °C, from **16** (3.83 g, 14.2 mmol) in a manner similar to that described for **18**, except that the reaction (stirring) time was 1.5 h. ^{1}H-NMR[14] ($CDCl_3$) δ: 1.55 (s, 9H, $C(CH_3)_3$), 1.74—1.91 (4H, m, 7-, 8-H), 2.04—2.12 (1H, m, 5-Ha), 2.20—2.26 (1H, m, 5-Hb), 2.69 (1H, m, 4-H), 2.93—2.99 (1H, m, 6-H), 3.75 (3H, s, OCH_3), 4.97 (1H, dd, J=3.4, 1.6 Hz, 1-H). ^{13}C-NMR[14] ($CDCl_3$) δ: 22.40 (t), 22.56 (t), 25.56 (t), 28.07 (q), 39.80 (d), 42.81 (d), 51.73 (d), 52.33 (q), 83.50 (s), 150.26 (s), 172.71 (s), 173.83 (s). IR ν_{max}^{KBr} cm^{-1}: 1735 (C=O), 1710 (C=O). MS *m/z*: 283 (M^+). *Anal.* Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.30; H, 7.31; N, 5.11.

2-*tert*-Butyl 6-Methyl (1*R,4*S**,6*S**)-3-Oxo-2-azabicyclo[2.2.2]octane-2,6-dicarboxylate (21)** This compound (3.89 g, 97%) was obtained as colorless prisms, mp 71—73 °C, from **17** (3.83 g, 14.2 mmol) in a manner similar to that described for **18**, except that the reaction (stirring) time was 3 h. ^{1}H-NMR[14] ($CDCl_3$) δ: 1.52 (s, 9H, $C(CH_3)_3$), 1.70—2.00 (5H, m, 5-Ha, 7-H, 8-H), 2.28—2.34 (1H, m, 5-Hb), 2.69 (1H, m, 4-H), 2.74—2.79 (1H, m, 6-H), 3.69 (3H, s, OCH_3), 4.97 (1H, m, 1-H). ^{13}C-NMR[14] ($CDCl_3$) δ: 22.30 (t), 26.10 (t), 26.13 (t), 27.97 (q), 39.57 (d), 42.05 (d), 52.22 (q), 82.98 (s), 150.28 (s), 173.10 (s), 173.39 (s). IR ν_{max}^{KBr} cm^{-1}: 1746 (C=O), 1712 (C=O). MS *m/z*: 283 (M^+). *Anal.* Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.46; H, 7.40; N, 4.91.

***c*-4-Amino-*r*-1,*t*-2,*t*-3-cyclohexanetricarboxylic Acid (22)** Compound **18** (617 mg, 1.81 mmol) was heated in AcOH (20 ml) and 6 M HCl at 50 °C for 21 d. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in a small amount of water. The aqueous solution was adjusted to pH 4 with 2 M NaOH, giving a white powder, which was recrystallized from water to give **22**·$2H_2O$ (416 mg, 86%) as a white powder, mp 214 °C (dec.). ^{1}H-NMR (2 M DCl) δ: 1.48—1.61 (1H, m, 5-Ha), 1.61—1.73 (1H, m, 6-Hb), 1.98—2.14 (2H, m, 5-Hb, 6-Ha), 3.11 (1H, dd, J=9.9, 4.8 Hz, 3-H), 3.27 (1H, q, J=3.7 Hz, 1-H), 3.77 (1H, dd, J=4.8, 3.7 Hz, 2-H), 3.86 (1H, dt, J=9.9, 4.0 Hz, 4-H). ^{13}C-NMR (2 M DCl) δ: 22.81 (t), 26.60 (t), 41.23 (d), 43.02 (d), 43.74 (d), 48.59 (d), 175.62 (s), 175.81 (s), 176.98 (s). IR ν_{max}^{KBr} cm^{-1}: 3581, 3496, 3409, 3248 (NH, OH), 1720 (C=O), 1697 (C=O). MS (FAB) *m/z*: 232 (M^++1). *Anal.* Calcd for $C_9H_{13}NO_6 \cdot 2H_2O$: C, 40.45; H, 6.41; N, 5.24. Found: C, 40.32; H, 6.13; N,

5.19.

***c*-4-Amino-*r*-1,*c*-2,*c*-3-cyclohexanetricarboxylic Acid (23)** Compound **19** (617 mg, 1.81 mmol) was treated in a manner similar to the conversion of **18** into **22**, giving **23**·1/2H_2O (365 mg, 84%) as a white powder, mp 214 °C (dec.). ^{1}H-NMR (2 M DCl) δ: 1.72 (1H, dq, J=3.7, 10.9 Hz, 6-Hb), 1.86—1.94 (1H, m, 5-Ha), 1.92—2.13 (2H, m, 5-Hb, 6-Ha), 2.77—2.84 (1H, m, 1-H), 3.19—3.21 (2H, m, 2-, 3-H), 3.98 (1H, d, J=2.2 Hz, 4-H). ^{13}C-NMR (2 M DCl) δ: 22.17 (t), 26.94 (t), 42.88 (d), 44.31 (d), 45.25 (d), 48.18 (d), 174.56 (s), 176.34 (s), 177.29 (s). IR ν_{max}^{KBr} cm^{-1}: 3448, 3412, 3112 (NH, OH), 1735 (C=O), 1700 (C=O). MS (FAB) *m*/*z*: 232 (M^++1). *Anal.* Calcd for $C_9H_{13}NO_6$·1/2H_2O: C, 45.00; H, 5.87; N, 5.83. Found: C, 45.20; H, 5.68; N, 5.85.

***c*-4-Amino-*r*-1,*t*-3-cyclohexanedicarboxylic Acid (24)** Compound **20** (512 mg, 1.81 mmol) was treated in a manner similar to the conversion of **18** into **22**, giving **24** (288 mg, 85%) as a white powder, mp 215 °C (dec.). ^{1}H-NMR (2 M DCl) δ: 1.55 (1H, dq, J=3.9, 12.1 Hz, 5-Ha), 1.64—1.67 (1H, m, 6-Hb), 1.69—1.74 (1H, m, 2-Hb), 2.01 (1H, dq, J=12.4, 3.7 Hz, 5-Hb), 2.06—2.16 (1H, m, 6-Ha), 2.41 (1H, dq, J=14.2, 2.9 Hz, 2-Ha), 2.80—2.84 (1H, m, 3-H), 2.85—2.87 (1H, m, 1-H), 3.48 (1H, dt, J=4.1, 11.0 Hz, 4-H). ^{13}C-NMR[14] (2 M DCl) δ: 25.13 (t), 26.82 (t), 28.83 (t), 29.00 (t), 38.09 (d), 38.13 (d), 42.94 (d), 50.10 (d), 50.93 (d), 176.56 (s), 178.71 (s). IR ν_{max}^{KBr} cm^{-1}: 3518, 3135, 3112 (NH, OH), 1739 (C=O), 1700 (C=O). MS (FAB) *m*/*z*: 188 (M^++1). *Anal.* Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.33; H, 6.75; N, 7.41.

***c*-4-Amino-*r*-1,*c*-3-cyclohexanedicarboxylic Acid (25)** Compound **21** (512 mg, 1.81 mmol) was treated in a manner similar to the conversion of **18** into **22**, giving **25**·2/3H_2O (296 mg, 82%) as a white powder, mp 240 °C (dec.). ^{1}H-NMR (2 M DCl) δ: 1.62 (1H, dq, J=3.9, 12.1 Hz, 6-Hb), 1.79—1.93 (3H, m, 5-Ha, 2-Hb, 6-Ha), 2.07 (1H, dq, J=10.6, 3.9 Hz, 5-Hb), 2.24 (1H, dt, J=10.6, 3.6 Hz, 2-Ha), 2.57—2.63 (1H, m, 1-H), 2.99 (1H, dt, J=11.9, 4.0 Hz, 3-H), 3.85 (1H, d, J=3.9 Hz, 4-H). ^{13}C-NMR[14] (2 M DCl) δ: 22.35 (t), 25.61 (t), 27.30 (t), 40.80 (d), 42.38 (d), 42.48 (d), 48.23 (d), 176.35 (s), 179.03 (s). IR ν_{max}^{KBr} cm^{-1}: 3567, 3373, 3234 (NH, OH), 1712 (C=O), 1685 (C=O). MS (FAB) *m*/*z*: 188 (M^++1). *Anal.* Calcd for $C_8H_{13}NO_4$·2/3H_2O: C, 48.24; H, 7.25; N, 7.03. Found: C, 48.29; H, 7.09; N, 6.93.

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