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 RuO₄ 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-piperidinetetra carboxylic acids and 2,3,5-piperidinetetra carboxylic acids with a cis-2,5-dicarboxy configuration from N-methoxy carbonyl-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. The intermediate products, isoquinuclidines 2–7, were dehalogenated by reaction with ethyl acetate, 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 ¹H-NMR analysis, in the analysis of 9, NOEs were observed between H³ and H⁷β between H⁷α and H¹⁰β, and –NOE was observed between H⁴α and H⁷β (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 trimethylsilyle iodide (Fig. 1) in CHCl₃, 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 SOCl₂–MeOH, and introductions of a Boc group were achieved by treatments with Boc₂O in CHCl₃, 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 CHCl₃, CHCl₃ 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 CHCl₃, 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 (RuO₄) oxidation. Under similar conditions employing AcOEt as a reaction solvent, compounds 14–17 disappeared after 2, 3, 5, 1, 3 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 RuO₄.

Finally, hydrolyses of lactams 18–21 were attempted. Treatments of 18 and 19 with 6 M HCl–AcOH at 50 °C for...
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 1H-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 H3 and H4 was 9.9 Hz and NOEs were observed between H3 and H5α and between H4 and H6β, the relative configuration of H3 and H4 proved to be trans-diaxial. As an NOE was observed between H4 and H6, the relative configuration of H3 and H4 proved to be cis. As an NOE was observed between H2 and H3 and no NOE was observed between H2 and H4, the relative configuration of H2 and H3 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 H3 and H4 was 2.2 Hz, the relative configuration of H3 and H4 proved to be cis. As NOEs were observed between H3 and H5α and between H3 and H5α and no NOE was observed between H2 and H3, the relative configurations between H1, H2 and H3 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 for 1 d, respectively, the 1H-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.

The stereochemistries of 24 and 25 were analyzed similarly to 22 and 23. In the case of 24, as the coupling constant between H3 and H4 was 11.0 Hz and NOEs were observed between H3 and H5α, between H2β and H4, and between H4 and H6β, the relative configuration of H1, H2 and H3 proved to be all cis. Thus compound 24 was identified as c-4-amino-r-1,c-2,c-3-cyclohexanetricarboxylic acid. In the case of 25, as the coupling constant between H3 and H4 was 3.9 Hz, the relative configuration of H3 and H4 proved to be cis. As NOEs were observed between H1, H2α, and H3, the relative configuration between H3 and H4 proved to be cis. Thus compound 25 was identified as c-4-amino-r-1,c-3-cy-
clohexanediacarbonyl acid.

In conclusion, we succeeded in stereospecifically synthesizing new 4-amino-1,2,3-clohexanetricarbonyl acids 22 and 23 as well as 4-amino-1,3-clohexanediacarbonyl 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 (CDCl₃) on a JEOL GSX-400 spectrometer using tetramethylsilane as an internal standard. For the amino acids, analysis was performed in 2 ml deuterium chloride (CDCl₃) using 1,4-dioxane as an internal standard at 300 MHz (1H) and 75.47 MHz (13C). NMR 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).

Tris-trimethylammonium dibenzoate (1R,4S,5R,6R)-2-Azabicyclo[2.2.2]octane-2,6-dicarboxylate (8) Compound 2 (870 mg, 3.07 mmol) was hydrolyzed 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 CH₂Cl₂ to give colorless prisms, m.p. 78–79 °C. 1H-NMR (CDCl₃) δ: 1.50–1.55 (1H, m, 7-H), 1.75–1.82 (1H, m, 7-H), 1.89–1.97 (2H, m, 7-H, 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, 5'-H), 3.17–3.20 and 3.25–3.28 (1H, m, 6-H, 6'-H), 3.39–3.44 (2H, m, 3-H, 4-H), 3.65 and 3.67 (6H, each s, 2 × OCH₃), 3.72 (3H, m, NO₂CH₃), 4.30 and 4.33 (1H, each dd, J = 4.0, 2.0 Hz, 1-H). 13C-NMR (CDCl₃) δ: 20.04 (t), 20.13 (t), 22.73 (t), 22.77 (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 νcm⁻¹: 3150, 1747 (C=O), 1698 (C=O). MS m/z: 285 (M⁺). Anal. Calc’d for C₁₇H₂₃NO₅: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.88; H, 6.61; N, 4.93.

Tris-trimethylammonium dibenzoate (1R,4S,5S,6S)-2-Azabicyclo[2.2.2]octane-2,6-dicarboxylate (9) Compound 3 (870 mg, 3.07 mmol) was hydrolyzed 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-Pr₂O to give colorless needles, m.p. 97–98 °C. 1H-NMR (CDCl₃) δ: 1.54–1.60 (2H, m, H, 8-H), 1.70–1.79 (1H, m, 7-H, 7'-H), 1.84–1.95 (1H, m, 7-H), 2.41 and 2.46 (1H, each dd, J = 5.6, 2.0 Hz, 4-H, 5-H), 3.20–3.25 (3H, m, 3-H), 3.30–3.35 (2H, m, 3-H, 5'-H, 3-H, 5'-H), 3.46–3.49 (1H, m, 4-H, 5'-H), 3.65 and 3.70 (6H, each s, 2 × OCH₃), 4.41 and 4.52 (1H, each dd, J = 4.0, 2.0 Hz, 1-H). 13C-NMR (CDCl₃) δ: 19.85 and 19.92 (2H, each d, J = 10.0 Hz, 1-H), 22.94 (t), 23.12 (t), 23.66 (t), 23.82 (t), 42.83 (d), 45.06 (d), 45.63 (d), 45.71 (d), 46.23 (d), 46.71 (d), 46.89 (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 νcm⁻¹: 3150, 1733 (C=O), 1693 (C=O). MS m/z: 285 (M⁺). Anal. Calc’d for C₁₇H₂₃NO₅: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.63; H, 6.82; N, 4.90.

2-Phenyl-6-(2-Phenylthiol) (1R,4S,5R,6R)-2-Azabicyclo[2.2.2]octane-2,6-dicarboxylate (10) Compound 4 (2.23 g, 6.37 mmol) was hydrolyzed 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. 1H-NMR (CDCl₃) δ: 1.55–1.58 (1H, m, 7-H, 8-H), 1.70–1.81 (4H, m, 5-H, 7-H, 8-H), 1.81–1.97 (1H, m, 4-H, 5-H), 2.11–2.14 (1H, m, 4-H, 5-H), 2.92–2.99 (1H, m, 6-H, 6'-H), 3.23–3.33 (2H, m, 3-H, 4-H), 3.68 (3H, m, OCH₃), 4.14–4.18 and 4.39–4.50 (5H, m, 1-H and 1'-CH₂CH₃), 6.88–6.97 (1H, m, 6-H and 6'-H), 7.20–7.30 (2H, m, aromatic H), 13C-NMR (CDCl₃) δ: 20.44 (t), 21.23 (t), 21.33 (t), 23.67 (t), 25.60 (t), 25.78 (d), 26.64 (t), 42.76 (d), 42.91 (d), 45.16 (d), 45.68 (d), 46.89 (t), 46.82 (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 νcm⁻¹: 3175 (C=O), 1693 (C=O). HR-MS m/z: Calcd for C₁₉H₁₇NO₄S: 333.1576 (M⁺). Found: 333.1574.

2-Methyl-6-(2-Phenylthiol) (1R,4S,5S,6S)-2-Azabicyclo[2.2.2]octane-2,6-dicarboxylate (11) Compound 5 (3.68 g, 11.11 mmol) was hydrolyzed 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. 1H-NMR (CDCl₃) δ: 1.57–1.63 (2H, m, 8-H, 8-H), 1.68–1.74 (2H, m, 5-H, 7-Ha), 1.91–2.00 (2H, m, 4-H, 7-Hb), 2.14–2.17 (1H, m, 5-Hb), 2.65–2.80 (6H, m, 6-H, 6'-H), 3.26–3.31 (1H, m, 3-Ha, 3-Hb), 3.40–3.43 (1H, m, 3-
m/z: Calcd for C_{14}H_{20}NO_{4}: 272.1682 (M·). Found: 272.1684.

2-butyl-5,6-Dimethyl (1R,4S,5S,6S,6R)-2-Azabicyclo[2.2.2]octane-2,6-dicarboxylate (18) This compound (14 (4.6 g, 14.2 mmol) in AcOEt (48 ml), RuO_{2}·H_{2}O (142 mg), and a 10% NaOCl 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_{2}SO_{4}, then concentrated under reduced pressure. The residual solid was recrystallized from iPr_{2}O to give 18 (1.75 g, 8.21 mmol) as colorless needles, mp 84 Vol. 53, No. 1 9.9, 4.0 Hz, 4-H). 13C-NMR (2 M DCl) δ: 1693 (C=O), 1697 (C=O), 1714 (C=O). HR-MS m/z: Calcd for C_{14}H_{21}NO_{5}: C, 59.35; H, 7.31; N, 5.11. Found: 59.30; H, 7.31; N, 5.11.

2-butyl-6-Methyl (1R,4S,5S,6S,6R)-3-Oxo-2-azabicyclo[2.2.2]octane-2,6-dicarboxylate (21) This compound (3.8 g, 14.2 mmol) in AcOEt (48 ml), RuO_{2}·H_{2}O (142 mg), and a 10% NaOCl 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_{2}SO_{4}, then concentrated under reduced pressure. The residual solid was subjected to column chromatography on silica gel (AcOEt), giving 19 (2.31 g, 93%) as a colorless oil. 1H-NMR (CDCl_{3}) δ: 1.52 (9H, s, C(CH_{3})_{3}), 1.57—1.86 (3H, m, 7-Ha, 8-H), 1.79—2.85 (1H, m, 6-H), 3.50 (3H, s, OCH_{3}), 4.50 (1H, m, 1-H). 13C-NMR (CDCl_{3}) δ: 21.07—21.15 (2H, m, 5-Hb, 6-Ha), 28.07 (1H, s, C(CH_{3})_{3}), 34.43 (1H, s, C(CH_{3})_{3}), 36.32 (1H, m, 2-H), 41.40 (1H, d, J = 5.5, 1.5 Hz, 4-H), 67.01 (1H, d, J = 5.5, 1.5 Hz, 4-H), 84.06 (1H, dd, J = 3.3, 1.5 Hz, 5-Ha). 13C-NMR (CDCl_{3}) δ: 18.43 (t), 21.56 (t), 27.80 (t), 29.76 (t), 41.73 (d), 42.30 (d), 44.91 (d), 52.34 (q), 52.37 (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} cm⁻¹: 1747 (C=O), 1714 (C=O). HR-MS m/z: Calcd for C_{14}H_{21}NO_{5}: 283.1475 (M⁺). Found: 283.1477.

2-butyl-6-Methyl (1R,4S,5S,6S,6R)-3-Oxo-2-azabicyclo[2.2.2]octane-2,6-dicarboxylate (20) This compound (3.8 g, 14.2 mmol) was treated in a manner similar to that described for 18, except that the reaction (stirring) time was 1.5 h. 1H-NMR (CDCl_{3}) δ: 1.52 (9H, s, C(CH_{3})_{3}), 1.70—2.00 (5H, m, 5-H, 6-H, 7-H, 8-H), 2.24—2.34 (2H, m, 5-Hb, 6-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). 13C-NMR (CDCl_{3}) δ: 22.30 (t), 26.10 (t), 26.13 (t), 27.97 (q), 39.75 (d), 42.05 (d), 52.22 (q), 82.98 (s), 150.28 (s), 173.10 (s), 173.39 (s). IR ν_{max} 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, 59.64; H, 7.40; N, 4.91.

c-4-Amino-r-1,2,2,3,3-pentahydroxytetraacetic Acid (22) Compound 18 (167.5 mg, 1.81 mmol) was heated in AcOH (20 ml) and 6 M HCl at 50°C for 21 h. 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 2H_{2}O to give 22 (416 mg, 86%) as a white powder, mp 214°C (dec.). 1H-NMR (2 M DCI) 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 = 3.7, 1.5 Hz, 7-H), 3.33 (1H, t, J = 3.7 Hz, 4-H), 3.78 (1H, t, J = 3.7 Hz, 4-H), 4.80 (1H, dd, J = 3.7, 1.5 Hz, 7-H), 4.98 (1H, s, C(CH_{3})_{3}), 6.92 (1H, d, J = 3.7 Hz, 3-H), 7.13 (1H, dd, J = 3.7, 1.5 Hz, 7-H), 7.82 (1H, d, J = 3.7 Hz, 3-H), 8.50 (1H, d, J = 3.7 Hz, 3-H). IR ν_{max} cm⁻¹: 3581, 3496, 3049, 3284 (NH, OH), 1720 (C=O), 1697 (C=O). MS (FAB) m/z: 232 (M⁺). Anal. Calcd for C_{12}H_{17}NO_5·2H_{2}O: C, 40.45; H, 6.41; N, 5.24. Found: C, 40.32; H, 6.13; N,
c-4-Amino-2,3-cyclohexanediacarboxylic 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): \(\delta\): 1.55 (1H, dq., \(J=3.9, 12.1\) Hz, 5-Ha), 1.64—1.67 (1H, m, 5-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: (2 M DCl): \(\delta\): 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), 175.35 (s), 178.30 (s). IR \(\nu_{\text{max}}^\text{cm}^{-1}\): 3518, 3135, 3112 (NH, OH), 1735 (C=O), 1703 (C=O). MS (FAB) m/z: 232 (\(M^+\)). Anal. Calcd for C\(_9\)H\(_{13}\)NO\(_6\)·1/2H\(_2\)O: C, 45.00; H, 5.87; N, 5.83. Found: C, 45.20; H, 5.68; N, 5.85.

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References and Notes
14) Some signals split or broaden due to the rotamers or the conformers.