We have previously reported a study of the synthesis of amino acids using Diels–Alder (D–A) adducts of dienes and N-containing dienophiles. 1,2) Subsequently, our interests turned to the synthesis of additional amino acids from other N-containing olefins, which can be prepared by pericyclic reaction.

In the present paper, we would like to report the synthesis of azetidine-cis-2,3-dicarboxylic acid (1) using the electrocyclic reaction of 1,2-dihydropyridine followed by ruthenium tetroxide oxidation. Bridges et al. reported the first synthesis of azetidine-2,3-dicarboxylic acids; their inhibition activities against the high affinity L-glutamate transporter were examined, but the details of the synthetic procedure and the physical data of the compounds were not described.3)

Bicyclic alkene 3, which can be transformed to certain useful compounds,4—11) is known to be easily prepared by a photoinduced electrocyclic reaction of 1-methoxy-1,2-dihydropyridine.4—8) As variation among yields has been frequently observed, depending on the irradiation conditions,12) compound 2 was exposed to UV rays using a high-pressure mercury lamp through a Pyrex filter, basically according to Fowler’s method,4) to give bicyclic alkene 3 in 85% yield. Oxidation of compound 3 by RuO4 was achieved at 0 °C for 80 h, giving the corresponding dicarboxylic acid, which was treated with diazomethane and isolated as dimethyl ester 4 in a 58% yield. Attempts at the hydrolysis of 4 with hydrochloric acid were made, but both treatments with 6 M HCl at 50 °C for 6 d and with 4 M HCl at 95 °C for 2 d afforded complicated mixtures of products (Chart 1). As the failure of these hydrolyses was attributed on one hand to the difficulty of removing the N-methoxycarbonyl group and on the other hand to the ease of epimerization, we planned to exchange the N-methoxycarbonyl group for an N-tert-butoxycarbonyl (Boc) group.

Although removal of the methoxycarbonyl group from compound 3 by methyl lithium has been reported,5,6) we newly executed a simple alkaline hydrolysis of 3 to achieve ease of handling. Compound 3 was heated with 2 M NaOH–EtOH under reflux for 24 h and the reaction mixture was treated with the ethereal solution of di-tert-butyl dicarbonate to give Boc form 5 in a 57% yield. The olefinic linkage of 5 was oxidized under similar conditions to those employed for the oxidation of 3, but both the disappearance of 5 and the completeness of the expected reaction appeared to be faster than those of 3. We concluded that the difference between the reaction rates was due to the solubilities of the intermediate products in AcOEt. The generated dicarboxylic acid was treated with diazomethane to give dimethyl ester 6 in a 67% yield (2 steps).

Compound 6 was heated with 6 M HCl–AcOH at 50 °C for 3 d and the salt of the target amino acid, which was obtained after concentration of the reaction mixture, and was desalted simply by dissolving the residue in hot water to give free amino acid 1 as colorless prisms in an 85% yield (Chart 2).

The stereochemistry of 1 was confirmed by observation of the coupling constants and the nuclear Overhauser effects (NOE) of the 1H-NMR analysis (Fig. 2). The coupling constant between H2 (δ 5.39) and H3 (δ 3.94) was 9.9 Hz, that...
between H3 and H11 (2: 1) to give 6 (600 mg, 67%) as a colorless oil. 1H-NMR (CDCl3) δ: 3.58 (3H, m, 1-H), 4.30 (1H, t, J=9.5 Hz, 2-H). 13C-NMR (CDCl3) δ: 28.32 (d), 45.78 (d). IR νmax cm⁻¹: 1754, 1712 (C=O). MS m/z: 273 (M⁺).

Azetidine-2,3,4,5-tetrahydroxylic acid (1) Compound 6 (100 mg, 0.366mol) was heated in AcOEt (10 ml) and 6% HCl (10 ml) at 50°C for 3 d. The reaction mixture was concentrated under reduced pressure. Addition of water (10 ml) to the residue and concentration of the solution were repeated three times. The residual solid was recrystallized from water to give amino acid 1 (45 mg, 85%) as colorless prisms, mp 187°C (dec.). 1H-NMR (13C DCl3) δ: 3.94 (1H, ddd, J=9.9, 9.9, 5.9 Hz, 3-H), 4.11 (1H, d, J=11.0, 5.9 Hz, 4-H), 4.31 (1H, dd, J=11.0, 9.9 Hz, 4-Ha), 5.39 (1H, d, J=9.9, 9.9 Hz, 4-Hb). 13C-NMR (13C DCl3) δ: 36.20 (d), 43.12 (t), 55.81 (d), 165.33 (s), 169.38 (s). IR νmax cm⁻¹: 3100 (N-H), 1746, 1640, 1590 (C=O). MS (FAB) m/z: 146 (M⁺+1). Anal. Calcd for C5H7NO4: C, 41.38; H, 4.86; N, 9.65. Found: C, 41.08; H, 4.78; N, 9.47.

References