A NEW SYNTHESIS OF OPTICALLY ACTIVE 2-METHOXYCARBONYL-4-AZETIDINONE FROM *L*-AZETIDINE-2-CARBOXYLIC ACID: UTILITY OF RUTHENIUM TETROXIDE OXIDATION

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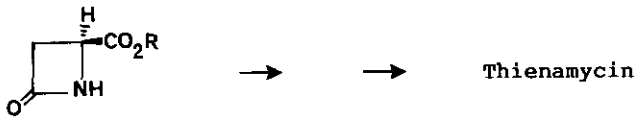
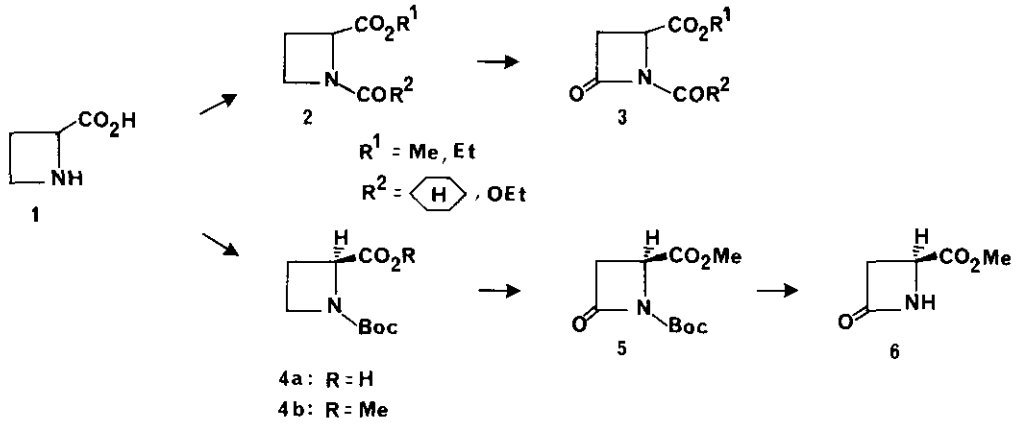
Abstract —— A first transformation of *L*-azetidine-2-carboxylic acid (**1**) into optically active monocyclic *N*-unsubstituted β-lactam, (2*S*)-2-methoxycarbonyl-4-azetidinone (**6**), has been developed *via* ruthenium tetroxide (RuO_4) oxidation process.

An optically active *N*-unsubstituted (NH-type) β-lactam, (2*S*)-4-azetidinon-2-carboxylic acid ester, have recently been shown to be promising intermediate for the synthesis of β-lactam antibiotics such as thienamycin and is prepared only by cyclization of *N*-silylated *L*-aspartic acid diester with Grignard reagent.[1,2]



However, little is known about the preparation of optically active 4-azetidinon-2-carboxylic acid ester from (2*S*)-azetidine-2-carboxylic acid. Previously, we reported the transformation[3] of *N*-acylated cyclic amines to the corresponding lactam derivatives by use of RuO_4 oxidation, in which *DL*-*N*-acylated azetidinon-2-carboxylic acid esters (**3**) were obtained in unsatisfactory yields varying from 17 to 34%. While, in order to obtain NH-type lactam derivatives, selective exocyclic deacylation of *N*-acylated lactams **3** obtained by RuO_4 oxidation is needed. But it is generally difficult to obtain NH-type lactams from *N*-acyllactams. More recently, we reported the efficient method[4] for preparing of NH-lactam type amino acid (*L*-pyroglutamic acid) *via* RuO_4 oxidation process in excellent yields by use of urethane-type *N*-protecting groups with the reverse system widely used in amino acid chemistry such as *p*-nitrobenzyloxycarbonyl [Z(NO_2)], *tert*-butyloxycarbonyl (Boc) and trichloroethoxycarbonyl (Troc) groups. Boc group was found to be

superior to the other two *N*-protecting groups in terms of both reactivity in oxidation process and deprotection. We wish to report here a new synthetic route to optically active 4-azetidinon-2-carboxylic acid methyl ester (**6**) from readily obtainable *L*-azetidine-2-carboxylic acid (**1**). For this work, we used the Boc group as *N*-protection of **1** due to the reason described above. The starting material, *L*-azetidine-2-carboxylic acid (**1**), was prepared from *L*-methionine *via* tosyl-*L*-homoserine lactone.[5] *N*-Protection of **1** with *tert*-butyl S-4,6-dimethylpyrimid-2-ylthiocarbonate[6] followed by esterification afforded the methyl *N*-Boc-*L*-azetidine-2-carboxylate (**4b**) in 93% yield from **1**. *N*-Boc-azetidine **4b** was oxidized with RuO_4 (small amount of RuO_2 hydrate—excess 10% aqueous sodium metaperiodate) in a two-phase system of ethyl acetate-water at room temperature for 72 h to give the corresponding β-lactam **5** in 73% yield. The structure of **5** was supported by the following data [Infrared (ir) spectrum ($CHCl_3$ solution) ν: 1820 cm^{-1} (lactam carbonyl); carbon 13 nuclear magnetic resonance (^{13}C-nmr) spectrum δ: 162.50 ppm (lactam carbonyl carbon)]. Finally, removal of Boc group of **5** by trifluoroacetic acid in CH_2Cl_2 at 0-5°C for 20 min gave the desired methyl *L*-4-azetidinon-2-carboxylate (**6**) in 85% yield. $[\alpha]_D^{19}$ -55.9° (*c*=1.26, $CHCl_3$).



To investigate the optical purity of **6** obtained above, **6** was hydrolyzed with 6*N* HCl to aspartic acid (83%), and its specific rotation was in good agreement with that of authentic *L*-aspartic acid.[7] The result indicated that racemization dose not occur throughout the RuO_4 oxidation process. Thus, the new synthetic route to optically active 2-methoxycarbonyl-4-azetidinone (**6**) from *L*-azetidine-2-carboxylic acid (**1**) has been developed. In addition, by employing this new simple pro-

cedure of RuO_4 oxidation, the compound **1** with optically active azetidine ring system will be useful as a versatile chiral building block for β-lactam antibiotics synthesis.

EXPERIMENTAL

Melting point were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (ir) spactra are recorded on a JASCO IRA-2 spectrometer. Mass spectra (ms) were measured on a JEOL JMS D-100 spectrometer. NMR spectra were obtained at 23°C using tetramethylsilane as an internal standard with a JEOL JNM-MH-100 or JEOL JNM-FX-100 spectrometer. Optical rotation were measured with a JASCO DIP-4 spectrometer.

L-Azetidine-2-carboxylic Acid (**1**). Prepared from *L*-methionine in 60% overall yield according to the reported procedure.[5] Colorless needles of mp 208-210°C (from 95% MeOH). $[\alpha]_D^{22}$ -118.5° (*c*=1.0, H_2O). [lit.[5] mp 210°C; $[\alpha]_D^{25}$ -120° (*c*=1, H_2O)].

N-tert-Butyloxycarbonyl-*L*-azetidine-2-carboxylic Acid (**4a**). A solution of *tert*-butyl S-4,6-dimethylpyrimidin-2-ylthiocarbonate (6.2 g, 26 mM) in dioxane (15 ml) was added to a mixture of **1** (2.0 g, 20 mM), triethylamine (6.2 g, 26 mM) and H_2O (15 ml), and then the mixture was stirred at room temperature for 24 h. To this mixture was added H_2O (30 ml) and the whole was extracted with AcOEt. The aqueous layer was acidified with 5*N* HCl under cooling, and then extracted with AcOEt. The AcOEt layer was washed with 5% HCl and brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to leave a colorless oil (3.7 g, 95%). ir (neat) ν: 3350, 1700 cm^{-1}. ms m/z: 201 (M^+). ^{1}H-nmr ($CDCl_3$) δ: 1.40 (9H, s, $C(CH_3)_3$), 1.99-2.71 (2H, m, C_3-H), 3.77-4.10 (2H, m, C_4-H), 4.68 (1H, dd, *J*=9, 6Hz, C_2-H), 9.32 (1H, s, CO_2H). $[\alpha]_D^{25}$ -97.8° (*c*=1.0, $CHCl_3$).

Methyl *N-tert*-Butyloxycarbonyl-*L*-azetidine-2-carboxylate (**4b**). A solution of **4a** (1.8 g, 9 mM) in EtOH (10 ml) was treated with diazomethane ethereal solution. The mixture was concentrated *in vacuo*, the resulting oil was purified by short column chromatography on SiO_2 with AcOEt-hexane (1:2, v/v) as an eluent to give **4b** (1.9 g, 98%) as a colorless viscous oil. ir ($CHCl_3$) ν: 1742, 1690 cm^{-1}. ms m/z: 215 (M^+). ^{1}H-nmr ($CDCl_3$) δ: 1.39 (9H, s, $C(CH_3)_3$), 2.10-2.73 (2H, m, C_3-H), 3.73 (3H, s, CO_2CH_3), 3.81-4.21 (2H, m, C_4-H), 4.63 (1H, dd, *J*=9, 3Hz, C_2-H). ^{13}C-nmr ($CDCl_3$) δ: 20.26 (t, C_3), 28.32 (q, $C(\underline{C}H_3)_3$), 47.66 (t, C_4), 52.15 (q, $CO_2\underline{C}H_3$),

60.59 (d, C_2), 80.08 (s, $CO_2\underline{C}(CH_3)_3$), 155.66 (s, $\underline{C}O_2C(CH_3)_3$), 172.16 (s, $\underline{C}O_2CH_3$). $[\alpha]_D^{22}$ -112.2° (*c*=1.0, $CHCl_3$).

Methyl *N*-*tert*-Butyloxycarbonyl-*L*-4-azetidinon-2-carboxylate (**5**). A solution of **4b** (1.2 g, 5.6 mM) in AcOEt (40 ml) was added to the mixture of RuO_2 hydrate (240 mg) and 10% aq. $NaIO_4$ (120 ml). The mixture was vigorously stirred by a mechanical stirrer at room temperature for 72 h in a sealed flask. The disappearance of the starting material was cheked by t.l.c (silica, AcOEt-hexane 1:2). The AcOEt layer was withdrawn, the aqueous layer was extracted with three-20 ml portions of AcOEt. The combined AcOEt solution was treated with isopropyl alcohol (2 ml) to destroy the RuO_4 oxidant. Black-colored RuO_2 which precipitated from the solution was filtered off and filtrate was washed with H_2O, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to leave a brown oil, which was purified by column chromatography on SiO_2 with AcOEt-hexane (1:2, v/v) as an eluent to give **5** (0.93 g, 73%) as a colorless oil. ir ($CHCl_3$) ν: 1820, 1750, 1730 cm^{-1}. ms m/z: 156 (M^+-$OCMe_3$), 128 (M^+-Boc). ^{1}H-nmr ($CDCl_3$) δ: 1.46 (9H, s, $C(CH_3)_3$), 2.97 and 3.30 (each 1H, each dd, *J*=16, 3Hz and *J*=16, 6Hz, C_3-H), 3.77 (3H, s, CO_2CH_3), 4.39 (1H, dd, *J*=6, 3Hz, C_2-H). ^{13}C-nmr ($CDCl_3$) δ: 27.98 (q, $C(\underline{C}H_3)_3$), 41.36 (t, C_3), 49.56 (d, C_2), 52.78 (q, $CO_2\underline{C}H_3$), 84.03 (s, $\underline{C}(CH_3)_3$), 147.07 (s, $\underline{C}O_2C(CH_3)_3$), 162.50 (s, C_4), 170.06 (s, $\underline{C}O_2CH_3$). $[\alpha]_D^{22}$ -74.5° (*c*=1.0, $CHCl_3$). *Anal*.Calcd for $C_{10}H_{15}NO_5$: C, 52.39; H, 6.60; N, 6.11. Found: C, 52.18; H, 6.48; N, 6.04.

Methyl *L*-4-Azetidinon-2-carboxylate (**6**). Trifluoroacetic acid (2 ml) was added to a solution of **5** (0.5 g, 2.2 mM) in CH_2Cl_2 (2 ml) and the mixture was stirred at room temperature for 20 mim. The reaction mixture was diluted with benzene (5 ml), and concentrated *in vacuo*. The residue was made alkaline with sat. $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to leave an oil, which was purified by column chromatography on SiO_2 with AcOEt-MeOH (20:1, v/v) as an eluent to give **6** (0.24 g, 85%) as a colorless oil. ir ($CHCl_3$) ν: 3425, 1778, 1745 cm^{-1}. ms m/z: 129 (M^+). ^{1}H-nmr ($CDCl_3$) δ: 3.03 and 3.33 (each 1H, each dd, *J*=16, 3Hz, and *J*=16, 6Hz, C_3-H), 3.74 (3H, s, CO_2CH_3), 4.19 (1H, dd, *J*=6, 3Hz, C_2-H), 7.03 (1H, br s, NH). ^{13}C-nmr ($CDCl_3$) δ: 43.21 (t, C_3), 47.02 (d, C_2), 52.44 (q, $CO_2\underline{C}H_3$), 167.13 (s, C_4), 171.92 (s, $\underline{C}O_2CH_3$). $[\alpha]_D^{19}$ -55.9° (*c*=1.26, $CHCl_3$). *Anal*.Calcd for $C_5H_7NO_3$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.48; H, 5.39; N, 10.80.

Hydrolysis of **6**. A solution of **6** (0.2 g, 0.15 mM) in 6*N* HCl (10 ml) was reflu-

xed for 4 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in 95% EtOH (10 ml). Pyridine (0.15 mM) was added to the solution under cooling. The mixture was allowed to stand at 5°C for 5 h to give a colorless powder of aspartic acid (0.17 g, 83%), mp 264-266°C. $[\alpha]_D^{20}$ +25.5° (*c*=0.76, 6*N* HCl). Its specific rotation was identical with that of authentic *L*-aspartic acid.[7]

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7) Optical rotation of authentic *L*-aspartic acid (Nakarai Chemical, Ltd.) used in this work: $[\alpha]_D^{20}$ +25.5° (*c*=0.76, 6*N* HCl). [lit.[8] $[\alpha]_D^{25}$ +33.8° (*c*=2, 5*N* HCl)].

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