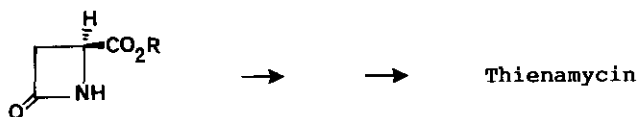


A NEW SYNTHESIS OF OPTICALLY ACTIVE 2-METHOXYCARBONYL-4-AZETIDINONE FROM
L-AZETIDINE-2-CARBOXYLIC ACID: UTILITY OF RUTHENIUM TETROXIDE OXIDATION

Ken-ichi Tanaka,* Shigeyuki Yoshifuji, and Yoshihiro Nitta
School of Pharmacy, Hokuriku University,
Kanagawa-machi, Kanazawa 920-11, Japan

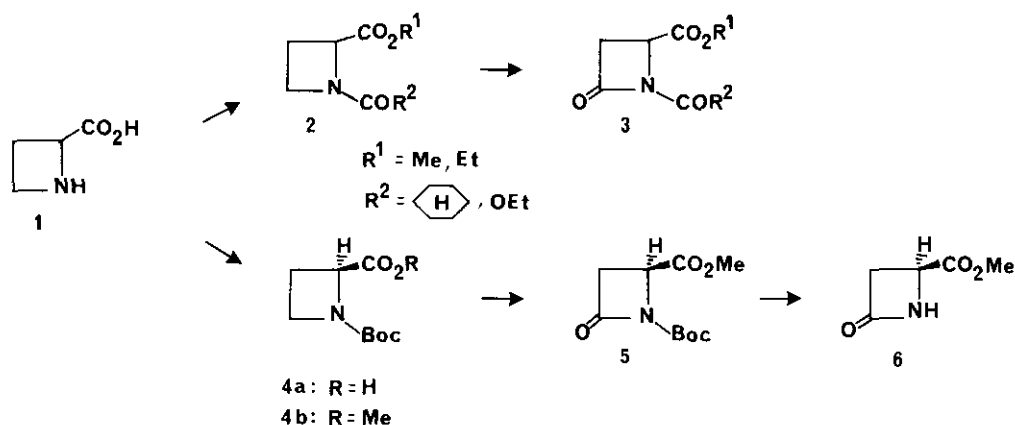
Abstract — A first transformation of *L*-azetidine-2-carboxylic acid (1) into optically active monocyclic *N*-unsubstituted β -lactam, (2*S*)-2-methoxycarbonyl-4-azetidinone (6), has been developed via ruthenium tetroxide (RuO_4) oxidation process.

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 transformation³ 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 method⁴ 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 [$\text{Z}(\text{NO}_2)$], *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-ylthiocarbonate⁶ 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 RuO₄ (small amount of RuO₂ 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 (CHCl₃ solution) ν : 1820 cm⁻¹ (lactam carbonyl); carbon 13 nuclear magnetic resonance (¹³C-nmr) spectrum δ : 162.50 ppm (lactam carbonyl carbon)]. Finally, removal of Boc group of **5** by trifluoroacetic acid in CH₂Cl₂ at 0-5°C for 20 min gave the desired methyl *L*-4-azetidinon-2-carboxylate (**6**) in 85% yield. [α]_D¹⁹ -55.9° (*c*=1.26, CHCl₃).



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 does not occur throughout the RuO₄ 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) spectra 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 5N 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^+). ^1H -nmr (CDCl_3) δ : 1.40 (9H, s, $\text{C}(\text{CH}_3)_3$), 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^+). ^1H -nmr (CDCl_3) δ : 1.39 (9H, s, $\text{C}(\text{CH}_3)_3$), 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, $\text{C}(\text{CH}_3)_3$), 47.66 (t, C_4), 52.15 (q, CO_2CH_3),

60.59 (d, C₂), 80.08 (s, CO₂C(CH₃)₃), 155.66 (s, CO₂C(CH₃)₃), 172.16 (s, CO₂CH₃). $[\alpha]_D^{22}$ -112.2° (c=1.0, CHCl₃).

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 RuO₂ hydrate (240 mg) and 10% aq. NaIO₄ (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 checked 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 RuO₄ oxidant. Black-colored RuO₂ which precipitated from the solution was filtered off and filtrate was washed with H₂O, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to leave a brown oil, which was purified by column chromatography on SiO₂ with AcOEt-hexane (1:2, v/v) as an eluent to give **5** (0.93 g, 73%) as a colorless oil. ir (CHCl₃) ν: 1820, 1750, 1730 cm⁻¹. ms m/z: 156 (M⁺-OCMe₃), 128 (M⁺-Boc). ¹H-nmr (CDCl₃) δ: 1.46 (9H, s, C(CH₃)₃), 2.97 and 3.30 (each 1H, each dd, J=16, 3Hz and J=16, 6Hz, C₃-H), 3.77 (3H, s, CO₂CH₃), 4.39 (1H, dd, J=6, 3Hz, C₂-H). ¹³C-nmr (CDCl₃) δ: 27.98 (q, C(CH₃)₃), 41.36 (t, C₃), 49.56 (d, C₂), 52.78 (q, CO₂CH₃), 84.03 (s, C(CH₃)₃), 147.07 (s, CO₂C(CH₃)₃), 162.50 (s, C₄), 170.06 (s, CO₂CH₃). $[\alpha]_D^{22}$ -74.5° (c=1.0, CHCl₃). Anal. Calcd for C₁₀H₁₅NO₅: 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 CH₂Cl₂ (2 ml) and the mixture was stirred at room temperature for 20 min. The reaction mixture was diluted with benzene (5 ml), and concentrated *in vacuo*. The residue was made alkaline with sat. NaHCO₃ and extracted with CHCl₃. The CHCl₃ 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 SiO₂ with AcOEt-MeOH (20:1, v/v) as an eluent to give **6** (0.24 g, 85%) as a colorless oil. ir (CHCl₃) ν: 3425, 1778, 1745 cm⁻¹. ms m/z: 129 (M⁺). ¹H-nmr (CDCl₃) δ: 3.03 and 3.33 (each 1H, each dd, J=16, 3Hz, and J=16, 6Hz, C₃-H), 3.74 (3H, s, CO₂CH₃), 4.19 (1H, dd, J=6, 3Hz, C₂-H), 7.03 (1H, br s, NH). ¹³C-nmr (CDCl₃) δ: 43.21 (t, C₃), 47.02 (d, C₂), 52.44 (q, CO₂CH₃), 167.13 (s, C₄), 171.92 (s, CO₂CH₃). $[\alpha]_D^{19}$ -55.9° (c=1.26, CHCl₃). Anal. Calcd for C₅H₇NO₃: 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 6N HCl (10 ml) was reflux-

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. $[\alpha]_D^{20} +25.5^\circ$ ($c=0.76$, 6*N* HCl). Its specific rotation was identical with that of authentic *L*-aspartic acid.⁷

REFERENCES AND NOTES

- 1) T. N. Salzmann, R. w. Ratcliffe, B. G. Christensen, and F. A. Bouffard, *J. Am. Chem. Soc.*, **102**, 6161 (1980).
- 2) P. J. Reider and E. J. J. Grabowski, *Tetrahedron Lett.*, **22**, 2293 (1982).
- 3) S. Yoshifuji, K. Tanaka, T. Kawai, and Y. Nitta, *Chem. Pharm. Bull.*, **33**, 5515 (1985).
- 4) S. Yoshifuji, K. Tanaka, T. Kawai, and Y. Nitta, *Chem. Pharm. Bull.*, in press.
- 5) M. Miyoshi, H. Sugano, T. Fujii, T. Ishihara, and N. Yoneda, *Chem. Lett.*, **1973**, 5, and references cited therein.
- 6) T. Nagasawa, K. Kuroiwa, K. Narita, and Y. Isowa, *Bull. Chem. Soc. Jap.*, **46**, 1269 (1973).
- 7) Optical rotation of authentic *L*-aspartic acid (Nakarai Chemical, Ltd.) used in this work: $[\alpha]_D^{20} +25.5^\circ$ ($c=0.76$, 6*N* HCl). [lit.⁸ $[\alpha]_D^{25} +33.8^\circ$ ($c=2$, 5*N* HCl)].
- 8) J. P. Greenstein and M. Minitz, "Chemistry of the Amino Acids," Vol. 1, John Wiley and Sons, Inc., New York, 1961.

Received, 30th April, 1986