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Chemical Conversion of Cyclic α-Amino Acids to α-Aminodicarboxylic Acids by Improved Ruthenium Tetroxide Oxidation[1)]

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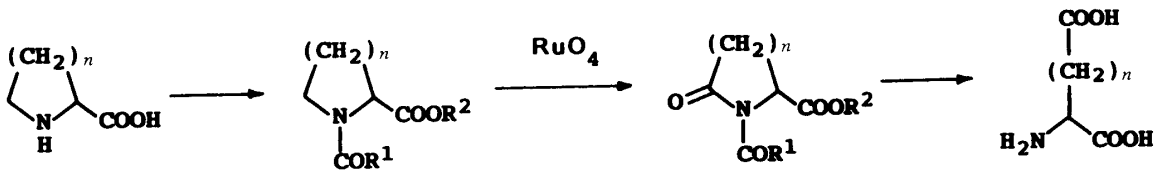
The ruthenium tetroxide (RuO_4) oxidation of *N*-acylated L-proline esters, prepared from L-proline, was carried out under two-phase conditions to afford good yields of the corresponding lactams with no appreciable racemization, and the products were hydrolyzed in aqueous hydrochloric acid to L-glutamic acid. Similar transformation starting with racemic 2-piperidinecarboxylic acid and 2-azetidinecarboxylic acid gave 2-aminoadipic acid and aspartic acid, respectively. A novel chemical conversion of cyclic α-amino acids into α-aminodicarboxylic acids has been accomplished. A new solvent system, ethyl acetate–water, was developed for this two-phase oxidation. It was found to be very useful in reducing the necessary reaction time.

Keywords——oxidation; regioselectivity; lactam synthesis; ruthenium tetroxide; cyclic α-amino acid; α-aminodicarboxylic acid; L-proline; L-glutamic acid; two-phase method; ethyl acetate–water system

Ruthenium tetroxide (RuO_4), introduced by Djerassi and Engle[2)] into organic chemistry in 1953, is well known as an effective multi-purpose oxidant.[3)] However, in contrast with the conversion of cyclic ethers to lactones,[3,4)] the RuO_4 oxidation of cyclic amines to lactams is unsuccessful in the *N*-unsubstituted compounds and gives only an intractable mixture.[5)] In 1974, Sheehan and Tulis[6)] demonstrated with simple cyclic amines that the *N*-acyl or *N*-sulfonyl derivatives could be mildly oxidized with RuO_4 to produce the corresponding lactams in good yields, and they suggested that RuO_4 oxidation should be a practical method for synthesizing lactams from cyclic amines. Since that time, Tortorella and co-workers[7)] have investigated the generality of the reaction. However, the utility of RuO_4 oxidation in the field of lactam synthesis has not yet been settled.

Although the regioselectivity in the RuO_4 oxidation of *N*-acylated cyclic amines having two oxidation sites next to the nitrogen atom, one of which is subject to carbonylation, has not been shown clearly, we applied this oxidation to the chemical conversion of cyclic α-amino acids into the corresponding α-aminodicarboxylic acids as shown in Chart 1. This chemical conversion, for example L-proline (**2**) into L-glutamic acid (**11**), is important and interesting both in organic chemistry and biochemistry since both amino acids are structurally closely related, but no effective oxidation method for pyrrolidine ring of the former (**2**) to the corresponding 2-pyrrolidinone is known. Therefore, the main step of the present conversion is the RuO_4 oxidation of *N*-acylated cyclic α-amino acid esters (**4**—**6**).

In general, there are two procedures for RuO_4 oxidation: one is a single-phase method using stoichiometric RuO_4 in inactive organic solvents such as chlorinated methanes and the other is a two-phase method employing a catalytic amount of RuO_2 in combination with a co-oxidant which serves to generate RuO_4 from the dioxide *in situ* in an organic solvent–water system. For the present work, we adopted the latter method, which is more economical and convenient. Thus, according to our standard procedure,[6)] *N*-acyl-L-proline esters (**5a**—**d**),



1: $n=1$
2: $n=2$
3: $n=3$

4: $n=1$, $R^2=Me$, Et
5: $n=2$, $R^2=Me$
6: $n=3$, $R^2=Et$

7: $n=1$, $R^2=Me$, Et
8: $n=2$, $R^2=Me$
9: $n=3$, $R^2=Et$

10: $n=1$
11: $n=2$
12: $n=3$

a: $COR^1=COCH_3$ **b**: $COR^1=COC_2H_5$ **c**: $COR^1=CO$-C$_6$H$_5$ **d**: $COR^1=COOEt$

Chart 1

readily prepared from commercial L-proline **2**, were initially oxidized at room temperature with a small amount of $RuO_2 \cdot$hydrate and an excess of 10% aqueous sodium metaperiodate in a two-phase system of carbon tetrachloride (or chloroform)–water. The reactions proceeded with a consistent yellow color, which indicates the existence of active RuO_4, and required long times to go to completion. After the reactions were completed, the desired lactams (**8a**—**d**) were isolated from the organic phase as the only product in high yields. The structures of the lactams were supported by the analytical and spectral data. No other oxidation product was detected. It was found that in the treatment of these cyclic amine derivatives having an ester group at the C-2 position with RuO_4, a regioselective oxidation occurs at the C-5 position without exception, possibly because of the ease of approach of RuO_4 oxidant to the oxidation site.

As the extremely long reaction time observed above reduces the practical value of the RuO_4 oxidation method in this field of lactam synthesis, we attempted to reduce it. From some considerations based on other experiments, we conjectured that a hydrophilic solvent might be more effective than the hydrophobic chlorinated methane, which is exclusively used as the organic solvent in the two-phase methods. Accordingly, we examined ethyl acetate which has only a little affinity for water and in which the two oxidants (RuO_4 and the co-oxidant) are stable.

During the planning of our work, Sharpless *et al.* reported an improved RuO_4 oxidation method for other types of compounds,[8] involving a new solvent system obtained by adding acetonitrile to the traditional two-phase system of carbon tetrachloride–water, based on their theory that acetonitrile might act as a ligand for the lower valent ruthenium metal. Therefore, we also tested their system with our substrates. Thus three solvent systems were compared under similar reaction conditions, and the results for the oxidation of L-proline derivatives are summarized in Table I (entries 1—13). Our ethyl acetate–water system significantly shortened the reaction time, but the Sharpless system was less effective in this respects.

The improved RuO_4 oxidation was extended to other cyclic α-amino acid derivatives. Racemic 2-piperidinecarboxylic acid (homoproline) derivatives (**6a**—**c**) were oxidized in the same way to afford the corresponding 2-piperidinones (**9a**—**c**) in good yields (Table I, entries 14—17). The common feature of both oxidations of proline and homoproline derivatives is that there is a great difference of reaction rate depending on the *N*-acyl group. As Sheehan and Tulis suggested (without any experimental data),[6] the reason may be the electronegativity of the *N*-acyl group. However, for our compounds having a substituent at the C-2 position, the steric factor of *N*-acyl group may also be important. When an acyl group is bulky, the coplanarity of the amide group is reduced and the basicity of the nitrogen atom increases; this factor may accelerate the reaction. In addition, there are two rotational isomers of the *N*-acyl derivatives of these amino acid esters[9] and it seems that the RuO_4 oxidant

TABLE I. RuO_4 Oxidation of *N*-Acylated Cyclic α-Amino Acid Esters

Entry	*n*	Substrate	COR^1	R^2	Solvent[a] system	Reaction time (h)	Product	Yield (%)
1	2	**5a**	$COCH_3$	CH_3	C	78	**8a**	91
2					S	72		89
3					A	22		96
4		**5b**	COC_2H_5	CH_3	C	69	**8b**	80
5					T	72		78
6					S	52		95
7					A	10		95
8		**5c**	COC_6H_{11}	CH_3	T	22	**8c**	92
9					S	17		84
10					A	3		98
11		**5d**	$COOC_2H_5$	CH_3	T	35	**8d**	84
12					S	22		79
13					A	6		99
14	3	**6a**	$COCH_3$	C_2H_5	A	14	**9a**	95
15		**6b**	COC_2H_5	C_2H_5	A	7.5	**9b**	92
16		**6c**	COC_6H_{11}	C_2H_5	A	4.5	**9c**	99
17		**6d**	$COOC_2H_5$	C_2H_5	A	6	**9d**	94
18	1	**4a**	$COCH_3$	CH_3	A	240[b]		
19		**4c**	COC_6H_{11}	C_2H_5	A	214	**7c**	33
20					A	24[c]		34
21					(CCl_4)[d]	168		30
22		**4d**	$COOC_2H_5$	CH_3	A	165	**7d**	17

a) Organic solvent–H_2O system. Organic solvent: C = $CHCl_3$; T = CCl_4; S = Sharpless system (CCl_4–CH_3CN); A = AcOEt. *b*) The reaction did not proceed. *c*) Four times the quantity of RuO_4 oxidant was used. *d*) A single-phase system was employed.

prefers to approach the C-5 (C-6 in the homoproline derivatives) position of one isomer, namely the one whose acyl carbonyl group faces the C-2 position, because there is no electrostatic repulsion between the oxidant and the oxygen atom of the acyl carbonyl group. Since the population of the isomer would increase in proportion to the size of the acyl group, a suitable bulky group may accelerate the oxidation reaction. In fact, *N*-cyclohexanecarbonyl derivatives (**5c**, **6c**) were oxidized fastest. However, further work remains necessary.

The analogous oxidation of *N*-acylated (±)-2-azetidinecarboxylic acid esters (**4a**, **c**, **d**) was unsuccessful. These reaction were very sluggish and decomposition of the products occurred due to hydrolysis by the acidic aqueous medium employed and/or overoxidation. The reaction of the *N*-acetyl compound **4a** practically did not progress. In some cases, as shown in Table I (entries 18—22), low yields of the desired β-lactam derivatives were obtained. An increase in the quantity of RuO_4 oxidant, or adoption of a single-phase method could shorten the reaction time but would not improve the yield.

Next, three kinds of lactams (**7c**, **8a**—**c**, **9c**) obtained from different amino acids were hydrolyzed in refluxing aqueous hydrochloric acid to convert them into α-aminodicarboxylic acids (**10**, **11**, **12**), which were shown to be identical with authentic (±)-aspartic acid, L-glutamic acid, and (±)-2-aminoadipic acid, respectively. The optical purity of L-glutamic acid obtained here was equal to that of the starting L-proline. This shows that the chirality at the C-2 position of the cyclic α-amino acid is not disturbed during the course of the RuO_4 oxidation. Thus, the chemical conversion of cyclic α-amino acids to linearchained α-aminodicarboxylic acids has been established.

The chemical conversion of cyclic α-amino acids as noted above extends the applicability

of the RuO_4 oxidation. This convenient and regioselective oxidation also raises the possibility of chemical modifications of natural or unnatural cyclic α-amino acids and peptides containing cyclic α-amino acid residues. Moreover, our two-phase method with the ethyl acetate–water system might be useful for the oxidative transformations of other types of organic compounds.

Experimental

All melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrometer. Mass spectra (MS) were measured on a JEOL JMS D-100 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained at 23 °C using tetramethylsilane as an internal standard with a JEOL JNM-MH-100 NMR spectrometer. Optical rotations were measured with a JASCO DIP-4 spectrometer.

Starting Materials for the RuO_4 Oxidation——1) Derivatives of 2-Azetidinecarboxylic Acid: 2-Azetidinecarboxylic acid was synthesized from γ-butyrolactone according to known procedures.[10,11] *N*-Acylated 2-azetidinecarboxylic acid esters were prepared by acylation with acyl chloride (cyclohexanecarbonyl chloride or ethyl chloroformate) in the presence of a base (aqueous NaOH or Na_2CO_3 solution) or with acetic anhydride, followed by esterification with methanolic or ethanolic hydrogen chloride (10% w/w).

2) Derivatives of L-Proline: All derivatives of L-proline were obtained by esterification of commercial L-proline[12] with MeOH–$SOCl_2$,[13] followed by acylation with acyl chloride or chloroformic acid ester under Schotten–Baumann acylation conditions.

3) Derivatives of 2-Piperidinecarboxylic Acid: *N*-Acyl-2-piperidinecarboxylic acid esters were prepared in a manner similar to that described above for the proline derivatives [esterification with EtOH–$SOCl_2$ and Schotten–Baumann acylation] from 2-piperidinecarboxylic acid which was obtained from 2-picolic acid by catalytic hydrogenation.[14]

These samples (**4**—**6**) for the RuO_4 oxidation were characterized as described below.

Methyl 1-Acetyl-2-azetidinecarboxylate (4a)——Obtained as a colorless oil, bp 112 °C (2 mmHg). MS *m/e*: 157 (M^+). IR ν_{max}^{film} cm^{-1}: 1641 (amide C=O), 1739 (ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.84 and 1.90 (3H, each s, rotational isomeric $NCOCH_3$), 2.06—2.86 (2H, m, C_3-H_2), 3.78 and 3.82 (3H, each s, rotational isomeric CO_2CH_3), 3.88—4.38 (2H, m, C_4-H_2), 4.60—4.86 (1H, m, C_2-H). *Anal.* Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.28; H, 7.12; N, 8.85.

Ethyl 1-Cyclohexanecarbonyl-2-azetidinecarboxylate (4c)——A colorless oil, bp 132 °C (2 mmHg). MS *m/e*: 239 (M^+). IR ν_{max}^{film} cm^{-1}: 1742 (ester C=O), 1650 (amide C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 3.86—4.42 (2H, m, C_4-H_2), 4.29 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.55—4.83 (1H, m, C_2-H). *Anal.* Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85; N, 5.85. Found: C, 65.02; H, 8.59; N, 5.60.

Methyl 1-Ethoxycarbonyl-2-azetidinecarboxylate (4d)——A colorless oil, bp 98 °C (1 mmHg). MS *m/e*: 187 (M^+). IR ν_{max}^{film} cm^{-1}: 1755 (ester C=O), 1712 (urethane C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 2.00—2.74 (2H, m, C_3-H_2), 3.78 (3H, s, CO_2CH_3), 3.84—4.24 (2H, m, C_4-H_2), 4.10 (2H, m, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.69 (1H, dd, J=10 and 6 Hz, C_2-H). *Anal.* Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.28; H, 7.20; N, 7.40.

Methyl L-1-Acetylprolinate (5a)——Obtained as a colorless oil, bp 113 °C (3 mmHg). $[\alpha]_D^{21}$ −101.7° (c=1.0, EtOH). MS *m/e*: 171 (M^+). IR ν_{max}^{film} cm^{-1}: 1740 (ester C=O), 1649 (amide C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.40 (4H, m, C_3-H_2 and C_4-H_2), 2.06 (3H, s, $NCOCH_3$), 3.40—3.80 (2H, m, C_5-H_2), 3.70 (3H, s, CO_2CH_3), 4.28—4.56 (1H, m, C_2-H). *Anal.* Calcd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18. Found: C, 56.01; H, 7.66; N, 8.21.

Methyl L-1-Propionylprolinate (5b)——A colorless oil, bp 100 °C (3 mmHg). $[\alpha]_D^{21}$ −105.9° (c=1.0, EtOH). MS *m/e*: 185 (M^+). IR ν_{max}^{film} cm^{-1}: 1740 (ester C=O), 1650 (amide C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7 Hz, $COCH_2C\underline{H}_3$), 1.70—2.40 (4H, m, C_3-H_2 and C_4-H_2), 2.35 (2H, q, J=7 Hz, $COC\underline{H}_2CH_3$), 3.30—3.80 (2H, m, C_5-H_2), 3.72 (3H, s, CO_2CH_3), 4.30—4.56 (1H, m, C_2-H). *Anal.* Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.21; H, 8.04; N, 7.39.

Methyl L-1-Cyclohexanecarbonylprolinate (5c)——A colorless oil, bp 147 °C (3 mmHg). $[\alpha]_D^{21}$ −86.9° (c=1.0, EtOH). MS *m/e*: 239 (M^+). IR ν_{max}^{film} cm^{-1}: 1743 (ester C=O), 1645 (amide C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.40—3.80 (2H, m, C_5-H_2), 3.72 (3H, s, CO_2CH_3), 4.32—4.57 (1H, m, C_2-H). *Anal.* Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85; N, 5.85. Found: C, 65.24; H, 9.01; N, 5.79.

Methyl L-1-Ethoxycarbonylprolinate (5d)——A colorless oil, bp 89 °C (2 mmHg). $[\alpha]_D^{15}$ −71.1° (c=1.0, EtOH). MS *m/e*: 201 (M^+). IR ν_{max}^{film} cm^{-1}: 1750 (ester C=O), 1700 (urethane C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.20 and 1.28 (3H, each t, each J=7 Hz, rotational isomeric $CO_2CH_2C\underline{H}_3$), 1.70—2.40 (4H, m, C_3-H_2 and C_4-H_2), 3.30—3.90 (2H, m, C_5-H_2), 3.73 (3H, s, CO_2CH_3), 4.19 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.28—4.47 (1H, m, C_2-H). *Anal.* Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.69; H, 7.38; N, 6.79.

Ethyl 1-Acetyl-2-piperidinecarboxylate (6a)——A colorless oil, bp 100 °C (2 mmHg). MS *m/e*: 199 (M^+). IR ν_{max}^{film} cm^{-1}: 1737 (ester C=O), 1650 (amide C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.14—2.44 (6H, m, C_3-H_2, C_4-H_2 and C_5-H_2), 2.14 (3H, s, $COCH_3$), 3.10—3.46 and 3.56—3.86 (each 1H, each m, C_6-H_2), 4.20 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.28—5.42 (1H, m, C_2-H). *Anal.* Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.15; H, 8.57; N, 7.02.

Ethyl 1-Propionyl-2-piperidinecarboxylate (6b)——A colorless oil, bp 110 °C (2 mmHg). MS *m/e*: 213 (M^+). IR ν_{max}^{film} cm^{-1}: 1740 (ester C=O), 1647 (amide C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, t, J=7 Hz, $COCH_2C\underline{H}_3$), 1.28 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.10—2.22 (6H, m, C_3-H_2, C_4-H_2 and C_5-H_2), 2.40 (2H, q, J=7 Hz, $COC\underline{H}_2CH_3$), 3.06—3.46 and 3.62—3.91 (each 1H, each m, C_6-H_2), 4.19 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 5.28—5.44 (1H, m, C_2-H). *Anal.* Calcd for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.57. Found: C, 61.87; H, 8.89; N, 6.55.

Ethyl 1-Cyclohexanecarbonyl-2-piperidinecarboxylate (6c)——A colorless oil, bp 143 °C (2 mmHg). MS *m/e*: 267 (M^+). IR ν_{max}^{film} cm^{-1}: 1740 (ester C=O), 1643 (amide C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 4.12 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 3.02—3.36 and 3.66—3.92 (each 1H, each m, C_6-H_2), 5.24—5.38 (1H, m, C_2-H). *Anal.* Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43; N, 5.24. Found: C, 67.27; H, 9.34; N, 5.20.

Ethyl 1-Ethoxycarbonyl-2-piperidinecarboxylate (6d)——A colorless oil, bp 99 °C (2 mmHg). MS *m/e*: 229 (M^+). IR ν_{max}^{film} cm^{-1}: 1740 (ester C=O), 1703 (urethane C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.25 and 1.27 (3H × 2, each t, each J= 7 Hz, two $CO_2CH_2C\underline{H}_3$), 1.10—2.39 (6H, m, C_3-H_2, C_4-H_2 and C_5-H_2), 2.77—3.21 dna 3.82—4.20 (each 1H, each m, C_6-H_2), 4.16 and 4.20 (2H × 2, each q, each J=7 Hz, two $CO_2C\underline{H}_2CH_3$), 4.70—4.86 (1H, m, C_2-H). *Anal.* Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.59; H, 8.20; N, 6.20.

Standard Procedure for the RuO_4 Oxidation of *N*-Acylated Amino Acid Esters (4a, c, d, 5a—d, and 6a—d) in a Two-Phase System——A solution of a substrate (12.0 mmol) to be oxidized in an organic solvent [CCl_4, $CHCl_3$ (EtOH free), AcOEt] (40 ml) or in the Sharpless system (CCl_4–CH_3CN, 1 : 1, v/v) (60 ml) was added to a mixture of $RuO_2 \cdot xH_2O$ (240 mg) (Aldrich Chemical Co.) and 10% aqueous $NaIO_4$ (120 ml) or the Sharpless system [$NaIO_4$ (11.0 g) and H_2O (45 ml)]. The mixture was vigorously stirred by a mechanical stirrer with a glass blade at room temperature. After the starting material had disappeared as determined by thin layer chromatography (TLC), the layers were separated. The aqueous layer was extracted with three 40-ml portions of the same organic solvent as used above, but with CH_2Cl_2 in the reaction under the Sharpless system. The combined organic solution was treated with isopropyl alcohol (2 ml) for 2—3 h to destroy the RuO_4 oxidant. Black-colored RuO_2 that precipitated from the solution was filtered off and the filtrate was washed with H_2O (40 ml), then dried over anhydrous Na_2SO_4. The solution was evaporated *in vacuo* to leave a residue, which was purified by column chromatography on silica-gel using AcOEt–hexane (1 : 2–2 : 1, v/v) as the eluent, and/or by vacuum distillation for oily substances or by recrystallization for the solid products.

The results of these oxidation experiments are summarized in Table I, and the oxidation products were characterized as described below.

RuO_4 Oxidation of Ethyl 1-Cyclohexanecarbonyl-2-azetidinecarboxylate (4c) in a Single-Phase System—— Excess of $RuO_2 \cdot xH_2O$ (1.00 g) was added to a mixture of CCl_4 (40 ml) and 10% aqueous $NaIO_4$ solution (120 ml). After vigorous stirring until the deep yellow color of RuO_4 was apparent, the CCl_4 layer was separated. The aqueous layer was extracted with two 20-ml portions of CCl_4 and the extracts were combined with the original CCl_4 solution. The substrate **4c** (2.70 g, 12.0 mmol) was added to this oxidant-containing solution, and the mixture was vigorously stirred at room temperature in a sealed flask until the yellow color faded. The resulting mixture was filtered and the filtrate was washed with saturated $NaHCO_3$ (20 ml), then dried over anhydrous Na_2SO_4. Evaporation of the solvent left a brown oil, which was purified by silica-gel column chromatography using AcOEt–hexane (1 : 1 and 2 : 1, v/v).

The results is listed in Table I. The product was identical (in terms of TLC, IR and NMR spectra) with a specimen prepared according to the standard procedure.

Ethyl 1-Cyclohexanecarbonyl-4-oxo-2-azetidinecarboxylate (7c)——Recrystallized from ether as colorless needles, mp 61—62 °C. MS *m/e*: 253 (M^+). IR ν_{max}^{film} cm^{-1}: 1812, 1755, 1690 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J= 7 Hz, $CO_2CH_2C\underline{H}_3$), 1.00—2.10 (11H, m, COC_6H_{11}), 2.92 (1H, dd, J=16 and 4 Hz, C_3-H), 3.24 (1H, dd, J=16 and 7 Hz, C_3-H), 4.19 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.33 (1H, dd, J=7 and 4 Hz, C_2-H). *Anal.* Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.52; H, 7.49; N, 5.50.

Methyl 1-Ethoxycarbonyl-4-oxo-2-azetidinecarboxylate (7d)——A colorless oil, bp 130 °C (1 mmHg, bath temp.). MS *m/e*: 201 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1819, 1738, 1698 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 2.97 (1H, dd, J=16 and 4 Hz, C_3-H), 3.29 (1H, dd, J=16 and 7 Hz, C_3-H), 3.74 (3H, s, CO_2CH_3), 4.29 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.42 (1H, dd, J=7 and 4 Hz, C_2-H). *Anal.* Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.75; H, 5.49; N, 6.89.

Methyl 1-Acetyl-5-oxoprolinate (8a)——Obtained as a colorless oil, bp 138 °C (2 mmHg). $[\alpha]_D^{15}$ −50.4° (c=1.0, EtOH). MS *m/e*: 185 (M^+). IR ν_{max}^{film} cm^{-1}: 1745, 1700 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.90 (4H, m, C_3-H_2 and C_4-H_2), 2.54 (3H, s, $NCOCH_3$), 3.80 (3H, s, CO_2CH_3), 4.81 (1H, dd, J=9 and 3 Hz, C_2-H). *Anal.* Calcd for $C_8H_{11}NO_4$: C, 51.88; H, 5.99; N, 7.56. Found: C, 51.60; H, 6.22; N, 7.43.

Methyl 1-Propionyl-5-oxoprolinate (8b)——A colorless oil, bp 116 °C (2 mmHg). $[\alpha]_D^{24}$ −53.2° (c=1.0, EtOH). MS *m/e*: 199 (M^+). IR ν_{max}^{film} cm^{-1}: 1740, 1700 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7 Hz, $COC\underline{H}_2CH_3$),

2.20—2.88 (4H, m, C_3-H_2 and C_4-H_2), 3.02 (2H, q, J=7 Hz, $COC\underline{H}_2CH_3$), 3.84 (3H, s, CO_2CH_3), 4.86 (1H, dd, J=9 and 3 Hz, C_2-H). *Anal.* Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.20; H, 6.59; N, 7.11.

Methyl 1-Cyclohexanecarbonyl-5-oxoprolinate (8c)——Recrystallized from petroleum ether as colorless plates, mp 70—71 °C. $[\alpha]_D^{14}$ −45.4° (c=1.0, EtOH). MS *m/e*: 253 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1750, 1695 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.00—1.92 and 3.30—3.68 (11H, m, COC_6H_{11}), 1.93—2.80 (4H, m, C_3-H_2 and C_4-H_2), 3.72 (3H, s, CO_2CH_3), 4.74 (1H, dd, J=9 and 3 Hz, C_2-H). *Anal.* Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.58; H, 7.54; N, 5.54.

Methyl 1-Ethoxycarbonyl-5-oxoprolinate (8d)——A colorless oil, bp 134 °C (2 mmHg). $[\alpha]_D^{15}$ −34.1° (c=1.0, EtOH). MS *m/e*: 215 (M^+). IR ν_{max}^{film} cm^{-1}: 1795, 1745, 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7 Hz, $NCO_2CH_2C\underline{H}_3$), 1.86—2.74 (4H, m, C_3-H_2 and C_4-H_2), 3.78 (3H, s, CO_2CH_3), 4.30 (2H, q, J=7 Hz, $NCO_2C\underline{H}_2CH_3$), 4.64 (1H, dd, J=9 and 3 Hz, C_2-H). *Anal.* Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.31; H, 6.22; N, 6.49.

Ethyl 1-Acetyl-6-oxo-2-piperidinecarboxylate (9a)——A colorless oil, bp 100 °C (2 mmHg). MS *m/e*: 213 (M^+). IR ν_{max}^{film} cm^{-1}: 1745, 1702 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.60—2.50 (6H, m, C_3-H_2, C_4-H_2 and C_5-H_2), 2.54 (3H, s, $COCH_3$), 4.20 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.88—5.02 (1H, m, C_2-H). *Anal.* Calcd for $C_{10}H_{15}NO_4$: C, 56.32; H, 7.09; N, 6.57. Found: C, 56.33; H, 7.06; N, 6.61.

Ethyl 1-Propionyl-6-oxo-2-piperidinecarboxylate (9b)——A colorless oil, bp 110 °C (2 mmHg). MS *m/e*: 227 (M^+). IR ν_{max}^{film} cm^{-1}: 1742, 1696 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7 Hz, $COCH_2C\underline{H}_3$), 1.28 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.64—2.72 (6H, m, C_3-H_2, C_4-H_2 and C_5-H_2), 3.00 (2H, q, J=7 Hz, $COC\underline{H}_2CH_3$), 4.14 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.90—5.04 (1H, m, C_2-H). *Anal.* Calcd for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16. Found: C, 58.09; H, 7.68; N, 6.08.

Ethyl 1-Cyclohexanecarbonyl-6-oxo-2-piperidinecarboxylate (9c)——A colorless oil, bp 141 °C (2 mmHg). MS *m/e*: 281 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1782, 1740, 1724 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 3.16—3.56 (1H, m, $COCH<$), 4.14 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.76—4.92 (1H, m, C_2-H). *Anal.* Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.04; H, 8.16; N, 4.88.

Ethyl 1-Ethoxycarbonyl-6-oxo-2-piperidinecarboxylate (9d)——Obtained as a colorless oil, bp 119 °C (2 mmHg). MS *m/e*: 243 (M^+). IR ν_{max}^{film} cm^{-1}: 1773, 1746, 1719 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.32 (3H, t, J=7 Hz, $NCO_2CH_2C\underline{H}_3$), 1.67—2.71 (6H, m, C_3-H_2, C_4-H_2 and C_5-H_2), 4.18 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.26 (2H, q, J=7 Hz, $NCO_2C\underline{H}_2CH_3$), 4.71—4.88 (1H, m, C_2-H). *Anal.* Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.29; H, 6.95; N, 5.77.

Hydrolysis of the Lactam Esters (7c, 8a—c, 9c) to the Amino Acids (10—12)——Solutions of the lactam esters (**7c**, **8a—c**, **9c**) (2.0 mmol) in 6 N hydrochloric acid (15 ml) were separately refluxed for 6 h. The reaction mixtures were evaporated and the residues were dissolved in H_2O (15 ml). The resulting solutions were treated with powdered K_2CO_3 (1.0 mmol) under cooling. The mixtures were allowed to stand at 5 °C for 20 h, leaving colorless crystals, which were identical (in terms of IR and NMR spectra) with the corresponding authentic samples.

(±)-Aspartic Acid (10)——Obtained from **7c** in 75% yield, mp 300 °C.

L-Glutamic Acid (11)——Obtained from **8a—c** in 82—90% yield. Sample from **8c**: mp 194—196 °C. $[\alpha]_D^{24}$ +30.4° (c=1.0, 5 N HCl) [lit.[15] $[\alpha]_D^{25}$ +32.2° (c=1.0, 5 N HCl)].

(±)-2-Aminoadipic Acid (12)——Obtained from **9c** in 71% yield, mp 192—194 °C. *Anal.* Calcd for $C_6H_{11}NO_4$: C, 44.71; H, 6.88; N, 8.69. Found: C, 45.03; H, 6.74; N, 8.51.

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References and Notes

1) A portion of this work was reported in a preliminary form by S. Yoshifuji, H. Matsumoto, K. Tanaka, and Y. Nitta, *Tetrahedron Lett.*, **1980**, 2963.
2) C. Djerassi and R. R. Engle, *J. Am. Chem. Soc.*, **75**, 3838 (1953).
3) D. G. Lee and M. van den Engh, "Oxidation in Organic Chemistry," ed. by W. S. Trahanovsky, Academic Press, New York, 1973, part B, Chapter 4.
4) A. B. Smith, III and R. M. Scarborough, Jr., *Synth. Commun.*, **10**, 205 (1980).
5) L. M. Berkowitz and P. N. Rylander, *J. Am. Chem. Soc.*, **80**, 6682 (1958).
6) J. C. Sheehan and R. W. Tulis, *J. Org. Chem.*, **39**, 2264 (1974).
7) *a*) F. Morlacchi, V. Losacco, and V. Tortorella, *J. Heterocycl. Chem.*, **16**, 297 (1979); *b*) G. Bettoni, G. Carbonara, C. Franchini, and V. Tortorella, *Tetrahedron*, **37**, 4159 (1981), and references cited therein.
8) P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, **46**, 3936 (1981).
9) *a*) H. Nishihara, K. Nishihara, T. Uefuji, and N. Sakota, *Bull. Chem. Soc. Jpn.*, **48**, 553 (1975); *b*) B. P. Roques, S. Combrisson, and R. Wasylishen, *Tetrahedron*, **32**, 1517 (1976); *c*) I. D. Rae and H. A. Scheraga, *Int. J. Peptide Protein Res.*, **13**, 304 (1979).

10) B. Wladislaw, *J. Org. Chem.*, **26**, 711 (1961).
11) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocycl. Chem.*, **6**, 435 (1969).
12) Optical rotation of L-proline (Sigma Chem. Co.) used in this work: $[\alpha]_D^{15}$ -55.3° ($c=1.0$, 5 N HCl) [lit.[15] $[\alpha]_D^{25}$ -60.4° ($c=1.0$, 5 N HCl)].
13) J. P. Greenstein and M. Minitz, "Chemistry of the Amino Acids," Vol. 1, John Wiley and Sons, Inc., New York, 1961.
14) M. Freifelder, *J. Org. Chem.*, **27**, 4046 (1962).
15) "Seikagaku Data Book," ed. by the Japanese Biochemical Society, Tokyo Kagaku Dohjin Co., Tokyo, 1979, p. 31.