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Synthesis of Optically Active Oxazolines from Optically Active Epoxides

Junko Umezawa,* Osamu Takahashi,† Keizo Furuhashi,† and Hiroyuki Nohira

Department of Applied Chemistry, Faculty of Engineering, Saitama University, Shimo-ohkubo, Urawa, Saitama 338, Japan,
†Pharmaceuticals & Biotechnology Laboratory, Japan Energy Corporation, Niizo-Minami, Toda, Saitama 338, Japan

Abstract: The reaction of optically active terminal epoxides, which were produced by a microbial reaction, with acetonitrile in the presence of a protic acid or Lewis acid was studied. 1,2-Epoxyoctane, 2-methyl-1,2-epoxyhexane, and pentafluorostyrene oxide gave the corresponding 4-substituted 2-methyl-2-oxazoline derivatives with moderate to excellent regioselectivity. The reactions proceeded with an inversion of the asymmetric center with high stereospecificity under $AlCl_3$- or $SnCl_4$-catalyzed conditions, while partial racemization occurred under HF- or CF_3SO_3H-catalyzed conditions. The acid used and the substituent on the epoxide affected the stereospecificity and regioselectivity of the oxazoline formation. 4-Hexyl-2-methyl-2-oxazoline obtained with high stereospecificity was converted into 2-aminooctanoic acid via 2-aminooctanol.

Introduction

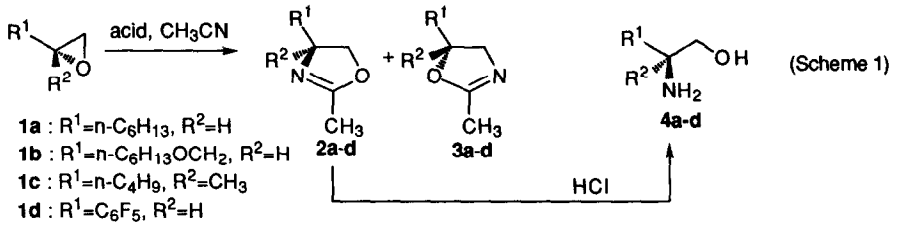
Oxazolines have been known to be useful for the synthesis of functionalized organic compounds.[1,2] In particular, Meyers et al. have demonstrated the utility of chiral 2-oxazolines for the asymmetric synthesis of optically active carboxylic acids, butyrolactones, alcohols, and thiiranes by using metalated 2-alkyloxazolines.[3] They prepared the starting chiral 2-alkyloxazolines from readily available amino diols. As a part of our continuing studies on the reactions of optically active terminal epoxides, which are readily produced by a microbial reaction, with various nucleophiles,[4~6] we found that the acid-catalyzed reaction of optically active epoxides with acetonitrile gave optically active 4-substituted 2-methyl-2-oxazolines. There is no detailed systematic study concerning the stereochemistry of oxazolines, obtained by the reaction of optically active terminal epoxides with nitriles, although several reaction mechanisms have been proposed for the reaction of racemic terminal epoxides.[7~9]

In this paper, we report on the synthesis of optically active oxazolines from optically active terminal epoxides and discuss the factors influencing the stereospecificity and regioselectivity of the formation of oxazolines, such as the acid catalyst used and the substituent on the epoxides. Moreover, we exemplify the application of the resultant 4-substituted 2-oxazoline in the synthesis of an unnatural optically active α-amino acid via an amino alcohol.

Results and Discussion

The optically active epoxides used in the present study were prepared by the microbial oxidation of the corresponding olefins as previously reported; four types of epoxides **1a~d** had optical purities greater than 90%ee.[4, 10~11] The reaction was performed by adding an epoxide into a mixture of a large excess of

acetonitrile and one equivalent of an acid. The reaction mixture was treated with aqueous sodium carbonate, after the complete consumption of the epoxide had been confirmed by GLC. The yield and the molar ratio of the resultant regioisomers, **2** and **3**, were calculated on the basis of the amount of the extract and purity determined by GLC, and the area ratio of another gas chromatogram, respectively. 4-Substituted 2-methyl-2-oxazoline **2** was isolated by column chromatography and hydrolyzed with dilute hydrochloric acid to give 2-amino alcohol **4**. The optical purity of **4** was determined by HPLC with a chiral stationary phase. The results are listed in Table 1.



1a : R^1=n-C_6H_{13}, R^2=H
1b : R^1=n-$C_6H_{13}OCH_2$, R^2=H
1c : R^1=n-C_4H_9, R^2=CH_3
1d : R^1=C_6F_5, R^2=H

2a-d **3a-d** **4a-d**

The reaction of **1a** with acetonitrile in the presence of HF, CF_3SO_3H, $AlCl_3$, or $SnCl_4$ gave 2-oxazolines, **2a** and **3a**, accompanied by the formation of halohydrin, diol, or ester. Although the reaction of **1a** with 1 equivalent of anhydrous HF was very slow (Entry 1), the addition of 10 equivalents of anhydrous HF resulted in completion of the reaction within 2.5 h (Entry 2). When concd. sulfuric acid was employed (Entry 5), only polymeric product was obtained, in contrast to the result of Oda et al.[7] In the presence of a protic acid such as HF and CF_3SO_3H (Entries 1~3, 8), the nitrogen atom of acetonitrile predominantly reacted with the more substituted carbon of **1a** to give 4-substituted 2-methyl-2-oxazoline **2a**, while the significant regioselectivity was not observed when a Lewis acid such as $AlCl_3$ or $SnCl_4$ was employed (Entries 9, 10). The absolute configuration of isolated **2a** was determined as *S* by comparing its optical rotation with that of an authentic sample.[12] This indicates that the back-attack of the nitrogen atom occurs with inversion of the asymmetric center. Hydolysis of **2a** gave 2-amino alcohol **4a** in quantitative yield. Optical purites of **4a** in Entries 2, 9, 10 indicate that the formation of 4-hexyl-2-metyl-2-oxazoline **2a** in the presence of HF, $AlCl_3$ and $SnCl_4$ proceeds with complete stereospecificity. However, the decrease of the optical purity of **4a** in Entry 8 indicates that a racemization process exists in the reaction of **1a** with acetonitrile in the presence of CF_3SO_3H.

The reaction of **1b~1d** with acetonitrile was also investigated in the presence of HF, CF_3SO_3H or $AlCl_3$. In contrast to the case of **1a**, the reaction of **1b** catalyzed by $AlCl_3$ gave 5-substituted 2-methyl-2-oxazoline **3b**, in which the nitrogen atom of acetonitrile was introduced into the less substituted carbon of **1b** with high regioselectivity (Entry 15). Epoxides **1c** and **1d** gave 4-substituted 2-methyl-2-oxazolines, **2c** and **2d**, with complete regioselectivity, independent on the kind of acid (Entries 17~21). The optical purities of the corresponding amino alcohols, **4c** and **4d**, derived from **2c** and **2d**, respectively, decreased, when HF or CF_3SO_3H was used in the oxazoline formation (Entries 17, 19 and 20).

The oxazoline formation from racemic epoxides has been demonstrated by several groups. Oda et al.[7] reported that the addition of nitriles to aliphatic epoxides in concetrated sulfuric acid at low temperature gave 2-oxazolines; in the reaction of propylene oxide with acetonitrile, 2,4-dimethyl-2-oxazoline was predominantly formed. They suggested an S_N1-like mechanism, which involved nucleophilic attack by the nitrile on a carbenium ion formed by the ring-opening of the protonated epoxide. Temnikova and Yandovski[8] emphasized that their oxazoline-formation reaction had to proceed through a carbenium ion,

Table 1. The reaction of various epoxides **1** with acetonitrile in the presence of various acids

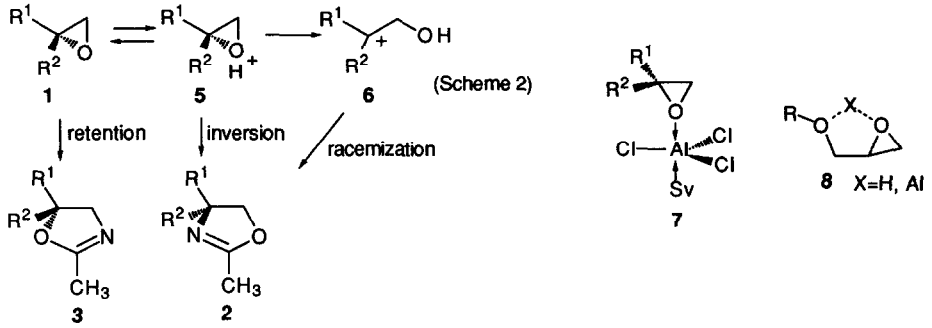
Entry	Epoxide	Acid [a] (eq.)	Temp. (°C)	Time (h)	Yield of **2** and **3** (%) [b]	**2** : **3** [c]	By-product	$[\alpha]_D^{25}$ of **2** (c 1.0, $CHCl_3$)	Optical purity of **4** (%ee)
1	**1a**	anhydrous HF (1)	rt	125	---- [d]	74 : 26	fluorohydrin		
2		anhydrous HF (10)	0	2.5	68	73 : 27	fluorohydrin	-85 [e]	91 [f]
3		aqueous HF (1)	0	1	22	74 : 26	diol		
4		concd. HCl (1)	0	1	0	------	chlorohydrin		
5		concd. H_2SO_4 (1)	0	4	0	------	polymer		
6		p-TsOH (1)	82	2	g)				
7		CF_3COOH (1)	rt	3.5	0	------	ester		
8		CF_3SO_3H (1)	rt	4.5	47	74 : 26	complicated	-53	53 [f]
9		$AlCl_3$ (1)	0	1	45	52 : 48	chlorohydrin	-85	91 [f]
10		$SnCl_4$ (1)	0	2	85	62 : 38	chlorohydrin	-85	91 [f]
11		$ZnCl_2$ (1)	rt	24	0	------	chlorohydrin		
12		LiCl (1)	rt	24	0	------	chlorohydrin		
13	**1b**	anhydrous HF (10)	0	1.5	91	27 : 73	fluorohydrin	-60	89 [f]
14		CF_3SO_3H (1)	0	2.5	0	------	complicated		
15		$AlCl_3$ (1)	0	1.5	39	0 : 100	chlorohydrin		
16	**1c**	anhydrous HF (10)	0	1.5	0	------	fluorohydrin polymer		
17		CF_3SO_3H (1)	0	1.5	45	100 : 0	high boiling product	-7.7	36 [f]
18		$AlCl_3$ (1)	0	2	66	100 : 0	high boiling product	-18	88 [f]
19	**1d**	anhydrous HF (10)	0	1	74	100 : 0	fluorohydrin	-76	35 [h]
20		CF_3SO_3H (1)	0	1	67	100 : 0	complicated	-57	23 [h]
21		$AlCl_3$ (1)	0	1.5	18	100 : 0	complicated		91 [h]

a) The molar ratio of the acid to the epoxides. b) Calculated on the basis of the amount of the extract and the purity of these isomers determined by GLC (3% SE-30 on Chromosorb WAW DMCS, 2m). c) Determined by GLC (15% DEGS on Uniport B, 2m). d) Not measured. e) See ref 12. f) Determined by HPLC (Enantio P1) of their acylamino esters. g) No reaction. h) Determined by HPLC (CROWNPAK CR(+)).

stabilized by dibutyl ether used as a solvent, and that the electronic character of the substituent of an epoxide influenced the regioselectivity in the reaction of 2,2-dimethylstyrene oxide with benzonitrile in the presence of $SnCl_4$. Shimizu and Yoshioka[9] showed that SiF_4 promoted the reaction of epoxides with nitriles to form 2-oxazoline with high regioselectivity, i.e., the nitrogen atom of the nitriles was introduced into the more substituted carbon of the epoxides, and that an electron-withdrawing group on the epoxide rings decreased the reactivity. They also suggested the oxazoline formation mainly proceeded through an S_N2 fashion but involved an S_N1 process on the basis of the result of the reaction using 4-t-butylcyclohexane derivatives.

The oxazoline formation in the present study using a protic acid as a catalyst is considered to proceed similarly to the hydrofluorination of terminal epoxides with an HF-amine reagent as previously reported;[6] the nucleophilic attack of acetonitrle would occur onto the free or protonated epoxides. Partial racemization

observed in the formation of **2a**, **2c**, and **2d** in the presence of a protic acid indicates that the reaction partially proceeds through carbenium ion **6**, as was suggested by Oda et al.[7] Polymerization and formation of high-boiling by-products (presumably oligomers) are also supposed to be caused by the formation of the carbenium ion. However, incomplete racemization implies the participation of another reaction route; the asymmetric carbon of protonated epoxide **5** is attacked from the back side by acetonitrile in an S_N2 fashion. The existence of both S_N1 and S_N2 fashions is compatible with the proposal of Shimizu and Yoshioka.[9] CF_3SO_3H is considered to offer free protons in higher concentration than HF does, and the oxazoline tends to be formed through the carbenium ion with higher probability in the presence of CF_3SO_3H. The substituent on the epoxides also affected the stereospecificity of the oxazoline formation. Protonated epoxides **5c** and **5d** would be easily transformed into highly stabilized carbenium ions **6**, a tertiary carbenium ion and a benzylic cation, resulting in the decrease of the optical purities of **2**.



The reaction of epoxides **1** with acetonitrile, catalyzed by a Lewis acid, such as $AlCl_3$ and $SnCl_4$, also gave the corressponding oxazolines. $AlCl_3$ and $SnCl_4$ would be solvated by acetonitrile, present in large excess in the reaction system, but could coordinate to the epoxides to form complexes **7**.[13] In these cases, the contribution of a carbenium ion intermediate similar to **6** is negligible, and nucleophilic attack by acetonitrile completely occurs on the asymmetric center of the epoxides from the back side, because the solvated Lewis acid blocks the front side. Subsequently, 4-substituted 2-methyl-2-oxazolines, **2a**, **2c**, and **2d**, were produced with high stereospecificity by using $AlCl_3$ as a Lewis acid.

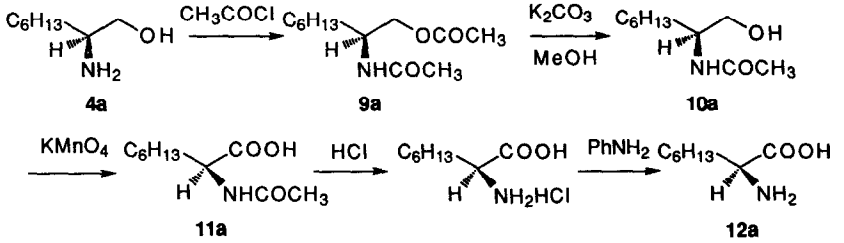
Although the regioselectivity in the oxazoline formation was complete for the reaction of **1c** and **1d**, the acid catalyst affected the regioselectivity for the reactions of **1a** and **1b**. This phenomenon can be explained as follows. When an epoxide is protonated by free proton, acetonitrile tends to attak at the more substituted epoxy carbon with low electron density to give **2**. However, since the electrophilicity of solvated $AlCl_3$ or $SnCl_4$ is lower than free proton, the attack of acetonitrile could occur on both epoxy carbons of intermediate **7**. When free epoxide **1** exists, acetonitrile favorably attacks at the less hindered epoxy carbon through an S_N2 fashion to give **3**.

In the case of **1b**, the major regioisomer changes to **3**, in contrast to the case of **1a** which gives **2** preferentially. The protonated and coordinated glycidyl ether could probably form the five-membered chelate **8** as an intermediate in addition to other possible intermediates **5**, **6**, and **7**. The ring-opening at CH_2-O in the epoxide would occur preferentially via intermediate **8** similar to the ring-opening of 2,3-epoxy alcohol with nucleophiles in the presence of Ti(O-i-Pr)4.[14]

The reaction system in the present study involves several kinds of nucleophiles other than acetonitrile, i.e., the conjugate base of a protic acid, the counter anion of a Lewis acid, and/or water. These nucleophiles

attack competitively to give halohydrins, esters, and/or diol. When the nucleophilicity of acetonitrile is higher than those of the coexisting nucleophiles, oxazolines were produced as main products, while oxazolines could not be obtained when the nucleophilicity of these coexisting nucleophiles is higher than that of acetonitrile, as observed in the reaction of **1a** in the presence of HCl or CF_3COOH. When benzonitrile was used instead of acetonitrile in the CF_3SO_3H-catalyzed reaction of **1a**, the reactivity of **1a** with the nitrile decreased to give the corresponding oxazoline in low yield, because of the lower nucleophilicity of benzonitrile with an electron-withdrawing phenyl group.

Next, we attempted to synthesize an unnatural α-amino acid from **2a**, obtained with high stereospecificity and regioselectivity in high yield (Entries 2), in order to demonstrate the utility of the resultant oxazolines. It is known that amino alcohols **4** can be converted into α-amino acids through protection of amino group, oxidation, and deprotection. For example, conversion of racemic 2-amino-1-propanol and 2-amono-1-butanol into the corresponding α-amino acids has been demonstrated by Billman and Parker;[15] the amino alcohols were protected by a benzoyl group and oxidized by $KMnO_4$ under basic conditions. However, when this procedure was applied to 2-amino-1-octanol **4a**, obtained by hydrolysis of **2a**, the oxidation did not take place, which would be probably due to the decreased hydrophilicity of the N-benzoylamino alcohol. Then, on the basis of the consideration, we changed the amino-protecting group to an acetyl group. Treatment of **4a** with acetyl chloride gave 2-(acetylamino)octyl acetate **9a**, which was converted into 2-(acetylamino)octanol **10a** by hydrolysis of the ester group in K_2CO_3/MeOH. Oxidation of **10a** by $KMnO_4$ was performed under neutral conditions in the presence of $MgSO_4$, because side reactions including deprotection easily occurred under basic or acidic conditions due to the instability of the acetyl group. Hydrolysis of 2-(acetylamino)octanoic acid **11a** with aqueous hydrochloric acid, followed by treatment with aniline, gave 2-aminooctanoic acid **12a**. By HPLC analysis of **12a**, it was confirmed that **12a** derived from **2a** was *L*-(*S*)-form with optical purity of 96%ee. Recrystallization of **12a** from water/EtOH resulted in the increase of its optical purity to 100%ee.



In summary, this paper has demonstrated that the sterospecificity and regioselectivity in the oxazoline formation by the reaction of optically active terminal epoxides with acetonitrile in the presence of a protic acid or Lewis acid are determined by the acid catalyst used and the substituent on the epoxides. A back-side attack by acetonitrile occurs on protonated or coordinated epoxides to give 4-substituted 2-methyl-2-oxazoline derivatives with high stereospecificity, while the formation of stable carbenium ions from the protonated epoxides results in partial racemization. The regioselectivity for the reaction of simple aliphatic epoxides was strongly affected by the type of an acid. This paper has also demonstrated that 4-hexyl-2-methyl-2-oxazoline with high optical purity is converted into the corresponding optically active α-amino acid via an amino alcohol.

Experimental Part

1. General remarks

Infrared spectra were recorded on a Shimazu IR-435. ^{1}H-NMR spectra were recorded on a Varian EM360L NMR spectrometer in $CDCl_3$ or CD_3OD at 24°C using TMS as an internal standard, or in D_2O at 24 °C using 3-(trimethylsilyl)propionic acid-d4 sodium salt as an internal standard. Mass spectra were obtained at a 70 eV ionization potential on a JEOL JMS DX-300. Elemental analysis was performed on a Perkin Elmer 240C. Optical rotations were measured at 25°C by Na D-line on an Union automatic digital polarimeter PM-201.

Optically active epoxides used in the present study were prepared by the microbial oxidation of the corresponding olefins.[4, 10~11] Acetonitrile was dried over molecular sieve 4A. Liquefied anhydrous hydrogen fluoride was dissolved in acetonitrile at -78°C in a teflon bottle before the reaction. Other reagents are of commercial origins.

The product of the reaction of an epoxide with acetonitrile was extracted under alkaline conditions. The extracted crude product was analyzed by GLC (2m, 3 % SE-30 on Chromosorb WAW DMCS) in order to calculate the yield of the regioisomeric oxazoline mixture on the basis of the peak area ratio of the isomers, halohydrin, diol, ester, and/or oligomeric by-products. The ratio of two regioisomers in the crude product was determined by GLC (2m, 15 % DEGS on Uniport B).

The optical purities of amino alcohols and α-amino acids were determined by HPLC with a chiral stationary phase. In order to determine the optical purities of 2-amino-1-octanol, 2-amino-3-hexyloxy-1-propanol, and 2-amino-2-methyl-1-hexanol by HPLC, the amino alcohols were converted into the corresponding acylamino esters by the reaction with 3,5-dinitrobenzoyl chloride (HPLC column, 4.6 mm ID × 25 cm TSK gel Enantio P1; Eluent, hexane : dichloroethane : ethanol = 60 : 35: 0.5; 1.0 ml / min; Detector, UV 254 nm). The optical purity of 2-amino-2-(pentafluorophenyl)ethanol was determined without any derivatization by HPLC (Column, 4.0 mm ID × 15 cm CROWNPAK CR(+); Eluent, aqueous perchloric acid; PH 1; 0.6 ml / min; Detector, UV 200 nm). The optical purity of 2-aminooctanoic acid was determined, as it was, by HPLC (Column, 4.6 mm ID × 25 cm CHIRALPAK WE; Eluent, 0.5 mM aqueous copper (II) sulfate; 1 ml / min; Detector, UV 254 nm). The absolute configuration of **2a** was confirmed by comparing its optical rotaion with that of an authentic sample.[12] The absolute configuration of **12a** was estimated by elution order in the HPLC analyses.

2. Oxazolines

4-Hexyl-2-methyl-2-oxazoline (**2a**) and **5-hexyl-2-methyl-2-oxazoline** (**3a**). To an HF/acetonitrile solution (1/1 mol/mol, 91.5 g, 1.5 mol) in a teflon bottle was added drop by drop (R)-(+)-1,2-epoxyoctane (19.2 g, 0.15 mol, $[\alpha]_D^{25}$ +14.4 (neat), 91%ee) under cooling with a dry ice-methanol bath, and the reaction mixture was stirred for 2.5 h at 0 °C. The reaction mixture was poured into saturated aqueous sodium carbonate (1800 ml) under cooling with an ice-water bath, and extracted with diethyl ether (3 × 600 ml). The combined organic layers were dried with anhydrous sodium sulfate and concentrated under reduced pressure. The remaining residue (20.2 g) was found to contain 4-hexyl-2-methyl-2-oxazoline and 5-hexyl-2-methyl-2-oxazoline (73:27) in 85% purity by GLC. Silica gel column chromatography (eluent: hexane/ethyl acetate 2/1) gave 8.20 g (32%) of 4-hexyl-2-methyl-2-oxazoline (**2a**) and 1.73 g (7 %) of 2-methyl-5-hexyl-2-oxazoline (**3a**) as colorless liquids. Characterization was accomplished after distillation. **2a**: Bp 88~92°C/8mmHg; $[\alpha]_D^{25}$ -85 (c 1.0, $CHCl_3$); IR 3350, 2900, 1680, 1460, 1380, 1250, 980, 900 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.9 (3H, bt), 1.0~1.6 (10H, m), 1.95 (3H, s), 3.6~4.5 (3H, m); MS (70 eV) m/z (relative intensities) 84 (100), 99 (44), 126 (9), 140 (20), 154 (2) [M-15], 169 (2) [M]. **3a**: Bp 75~80°C/1mmHg (glass tube oven), $[\alpha]_D^{25}$ +45 (c 1.0, $CHCl_3$); IR 3400, 2900, 2850, 1670, 1460, 1390, 1220, 960 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.9 (3H, bt), 1.0~1.8 (10H, m), 1.95 (3H, t), 3.0~4.1 (2H, m), 4.1~4.7 (1H, m).

2-Methyl-4-(2-oxaoctyl)-2-oxazoline (**2 b**) and **2-methyl-5-(2-oxaoctyl)-2-oxazoline** (**3b**). To an HF/acetonitrile solution (1/1 mol/mol, 61.0 g, 1.0 mol) in a teflon bottle was added drop by drop (R)-(+)-glycidyl hexyl ether (15.8 g, 0.10 mol, $[\alpha]_D^{25}$ +9.2 (neat), 90%ee) under cooling with a dry ice-methanol bath, and the reaction mixture was stirred for 1.5 h at 0 °C. The reaction mixture was poured into saturated aqueous sodium carbonate (1200 ml) under cooling with an ice-water bath, and extracted with diethyl ether (3 × 600 ml). The combined organic layers were dried with anhydrous sodium sulfate and concentrated under reduced pressure. The remaining residue (20.0 g) was found to contain 2-methyl-4-(2-oxaoctyl)-2-oxazoline and 2-methyl-5-(2-oxaoctyl)-2-oxazoline (27:73) in 91% purity by GLC. Silica gel column

chromatography (eluent: hexane/ethyl acetate 1/5) gave 1.84 g (9%) of 2-methyl-4-(2-oxaoctyl)-2-oxazoline (**2b**) and 3.15 g (16 %) of 2-methyl-5-(2-oxaoctyl)-2-oxazoline (**3b**) as colorless liquids. Characterization was accomplished after distillation. **2b**: Bp 80~88°C/1mmHg (glass tube oven); $[\alpha]_D^{25}$ -60 (c 1.0, $CHCl_3$); IR 3500, 2970, 1650, 1370, 1220, 1100, 980 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.9 (3H, bt), 1.0~1.8 (8H, m), 2.0 (3H, s), 3.2~3.8 (4H, m), 4.0~4.5 (3H, m); MS (70 eV) m/z (relative intensities) 55 (100), 84 (26), 126 (6), 140 (3), 154 (1) [M-15], 169 (4) [M]. **3b**: Bp 80~88°C/1mmHg (glass tube oven); $[\alpha]_D^{25}$ +38 (c 1.0, $CHCl_3$); IR 3500, 2900, 2850, 1670, 1450, 1390, 1220, 1110 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.9 (3H, bt), 1.0~1.8 (8H, m), 2.0 (3H, t), 3.2~4.2 (6H, m), 4.4~5.0 (1H, m).

4-Butyl-2,4-dimethyl-2-oxazoline (2c). To a dispersion of anhydrous $AlCl_3$ (3.3 g, 25 mmol) in acetonitrile (10.3 g, 250mmol) was added drop by drop (R)-(-)-2-methyl-1,2-epoxyhexane (2.85 g, 25 mmol, $[\alpha]_D^{25}$ -9.3 (neat), 90%ee) under cooling with an ice-water bath, and the reaction mixture was stirred for 2 h at 0 °C. The reaction mixture was poured into saturated aqueous sodium carbonate (85 ml) and extracted with diethyl ether (3 × 100 ml). The combined organic layers were dried with anhydrous sodium sulfate and concentrated under reduced pressure. The remaining residue (3.11 g) was found to contain 4-butyl-2,4-dimethyl-2-oxazoline in 83% purity by GLC. Distillation gave 1.58 g (41%) of 4-butyl-2,4-dimethyl-2-oxazoline (**2c**) as a colorless liquid: Bp 100~110°C/21mmHg (glass tube oven); $[\alpha]_D^{25}$ -18 (c 1.0, $CHCl_3$); IR 2900, 1660, 1250 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.9 (3H, bt), 1.0~1.8 (9H, m), 2.0 (3H, s), 3.8 and 4.0 (AB, J = 8 Hz).

2-Methyl-4-pentafluorophenyl-2-oxazoline (2d). To a solution of CF_3SO_3H (1.76 ml, 20 mmol) in acetonirtile (8.1 g, 200 mmol) was added drop by drop (R)-(+)-pentafluorostyrene oxide (4.20 g, 20 mmol, $[\alpha]_D^{25}$ +2.5 (neat), 97%ee) under cooling with an ice-water bath, and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was poured into saturated aqueous sodium carbonate (30 ml) and extracted with diethyl ether (3 × 50 ml). The combined organic layers were dried with anhydrous sodium sulfate and concentrated under reduced pressure. The remaining residue (4.06 g) was found to contain 2-methyl-4-pentafluorophenyl-2-oxazoline in 83% purity by GLC. Silica gel column chromatography (eluent: hexane/ethyl acetate 3/1) gave 1.87 g (37%) of 2-methyl-4-pentafluorophenyl-2-oxazoline (**2d**) as a colorless liquid. Characterization was accomplished after distillation. Bp 75~80°C/1mmHg (glass tube oven); $[\alpha]_D^{25}$ -57 (c 1.0, $CHCl_3$); IR 3400, 2900, 1650, 1480, 1420, 1380, 1350, 1220, 1120, 1050, 950 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 2.1 (3H, s), 4.1~4.8 (2H, m), 5.5 (1H, t, J = 8.5 Hz).

3. Amino alcohols

A miture of oxazoline **2** (100 mg) and 3N HCl (0.5 ml) was stirred for 3 h at 100 °C. The reaction mixture was cooled down to room temperature, diluted with 20 ml of water, poured into 3N NaOH (1 ml), and extracted with diethyl ether (2 × 20 ml). The combined organic layers were dried with anhydrous sodium sulfate and concentrated under reduced pressure to give amino alcohol **4**.

2-Amino-1-octanol (4a): IR 3350, 2850, 1580, 1460, 1370, 1030 cm^{-1}; ^{1}H-NMR δ (CD_3OD) 0.9 (3H, bt), 1.0~1.6 (10H, m), 2.5~3.0 (1H, m), 3.0~3.9 (2H, m), 4.8 (3H, s); MS (70 eV) m/z (relative intensities) 55 (21), 60 (24), 114 (100) [M-31].

2-Amino-3-hexyloxy-1-propanol (4b): ^{1}H-NMR δ (CD_3OD) 0.9 (3H, bt), 1.0~1.9 (8H, m), 2.8~3.2 (1H, m), 3.2~3.8 (6H, m), 4.7 (3H, s).

2-Amino-2-methyl-1-hexanol (4c): IR 3200, 2850, 2450, 1580, 1450, 1370, 1030 cm^{-1}; ^{1}H-NMR δ (CD_3OD) 1.0 (6H, m), 1.1~1.6 (6H, m), 3.3 (2H, s), 4.8 (3H, s); MS (70 eV) m/z (relative intensities) 74 (21), 100 (100) [M-31].

2-Amino-2-(pentafluorophenyl)ethanol (4d): ^{1}H-NMR δ (CD_3OD) 3.8 (2H, d, J = 6 Hz), 4.4 (1H, t, J = 7 Hz), 4.7 (3H,.s); MS (70 eV) m/z (relative intensities) 99 (3), 177 (1), 196 (100) [M-31].

4. Amino acid

(S)-2-(Acetylamino)octyl acetate (9a). To a mixture of (S)-(+)-2-amino-1-octacnol **4a** (1.02 g, 7 mmol, 91%ee), triethylamine (5.4 ml, 39 mmol), and diethyl ether (70 ml) was added drop by drop acetyl chloride (2.5 ml, 35 mmol) under cooling with a water bath, and the reaction mixture was stirred for 3 h at room temperature under nitrogen. The reation mixure was poured into water (150 ml) and extracted with dichloromethane (2 × 150 ml). The combined organic layers were washed with aqueous sodium chloride (2 × 150 ml), dried with anhydrous magnesium sulfate, and concentrated under reduced pressure to give 1.60 g (100%) of (S)-2-(acetylamino)octyl acetate (**9a**): ^{1}H-NMR δ ($CDCl_3$) 0.9 (3H, bt), 1.0~1.7 (10H, m), 1.95 (3H, s), 2.05 (3H, s), 4.1 (2H, m), 4.0~4.5 (1H, m), 5.4~5.8 (1H, m).

(S)-2-(Acetylamino)octanol (10a). A mixture of (S)-2-(acetylamino)octyl acetate (1.58 g, 6.9 mmol), anhydrous potassium carbonate (4.28 g, 31 mmol), and methanol (65 ml) was stirred for 17 h at room temperature. To the reaction mixture was added 5% sodium hydrogen carbonate (100 ml) and extracted with dichloromethane (2 × 100 ml). The combined organic layers were washed with aqueous sodium chloride (100 ml), dried with anhydrous magnesium sulfate, and concentrated under reduced pressure to give 0.85 g (66%) of (S)-2-(acetylamino)octanol (**10a**): ^{1}H-NMR δ ($CDCl_3$) 0.9 (3H, bt), 1.0~1.8 (10H, m), 2.0 (3H, s), 3.5~3.8 (2H, m), 3.6~4.1(1H, m), 4.2 (1H, s), 6.8 (1H, d, J = 8.5 Hz).

(S)-2-(Acetylamino)octanoic acid (11a). A mixture of (S)-2-(acetylamino)octanol (290 mg, 1.6 mmol), anhydrous magnesium sulfate (20 mg), potassium permanganate (330 mg, 2.1 mmol), and water (10 ml) was stirred for 2 h at 60 °C. The mixture was cooled down to room temperature, and aqueous sodium hydrogen sulfite (5ml) was added to dissolve brown solid. The aqueous solution was acidified with concd. hydrochloric acid (PH < 1) and extracted with diethyl ether (3 × 20 ml). The combined organic layers were dried with anhydrous sodium sulfate and concentrated under reduced pressure. Silica gel column chromatography (eluent: dichloromethane/ethanol 9/1) gave 150 mg (46%) of (S)-2-(acetylamino)octanoic acid (**11a**): IR 3300, 2900, 1700, 1600, 1440, 1200 cm^{-1}; ^{1}H-NMR δ (CD_3OD) 1.0 (3H, bt), 1.1~1.7 (10H, m), 2.1 (3H, s), 4.3~4.7 (1H, m), 4.8 (1H, s); MS (70 eV) m/z (relative intensities) 43 (100), 56 (23), 60 (19), 85 (28), 99 (34), 114 (83), 141 (4), 156 (29) [M-45], 183 (3) [M-18], 201 (1) [M].

(S)-2-Aminooctanoic acid (12a). A mixture of (S)-2-(acetylamino)octanoic acid (150 mg, 0.74 mmol) and 5N HCl (1.2 ml) was stirred for 5.5 h at 100 °C and then cooled down to room temperature. The precipitate was dissolved in water (3ml) and concentrated to remove excess HCl. In order to remove water completely, azeotropic evaporation with ethanol (3ml) was repeated for three times. To an ethanol (1.2 ml) solution of the resulted white solid was added aniline (1ml) to get free amino acid and stored in refrigerator for 1 h. The white precipitate was collected by filtration, washed with cooled ehtanol (2 ml), and dried in vacuo for 1 h at 50 °C to give 60 mg (51%) of (S)-2-aminooctanoic acid (**12a**) (96%ee). Recrystalization from water/ethanol gave 40 m g (100%ee) of white needle: ^{1}H-NMR δ (D_2O, NaOD) 0.9 (3H, bt), 1.1~1.7 (10H, m), 3.3 (1H, m), 4.9; C 60.00, H 11.00, N 8.63 (Calcd. C 60.38, H 10.69, N 8.81); $[\alpha]_D^{25}$ +21 (c 0.3, 1N HCl).

References

1. R. H. Wiley, L. L. Bennett, Jr., *Chem. Rev.*, 1949, **44**, 447.
2. J. A. Frump, *Chem. Rev.*, 1971, **71**, 483.
3. A. I. Meyers, E. D. Mihelich, *Angew. Chem. Int. Ed. Engl.*, 1976, **15**, 270.
4. O. Takahashi, J. Umezawa, K. Furuhashi, M. Takagi, *Tetrahedron Lett.*, 1989, **30**, 1583.
5. M. Fukumasa, K. Furuhashi, J. Umezawa, O. Takahashi, T. Hirai, *Tetrahedron Lett.*, 1991, **32**, 1059.
6. J. Umezawa, O. Takahashi, K. Furuhashi, H. Nohira, *Tetrahedron Asymmetry*, 1993, **4**, 2053.
7. R. Oda, M. Okano, S. Tokiura, F. Misumi, *Bull. Chem. Soc. Jpn.*, 1962, **35**, 1219.
8. T. I. Temnikova, V. N. Yandovski, *Zh. Org. Khim.*, 1968, **4**, 178.
9. M. Shimizu, H. Yoshioka, *Heterocycles*, 1988, **27**, 2527.
10. K. Furuhashi, M. Shintani, M. Takagi, *Appl. Microbiol. Biotecnol.*, 1986, **23**, 218.
11. K. Furuhashi, *J. Synth. Org. Chem. Jap.*, 1987, **45**,162.
12. a) A. Toshimitsu, S. Uemura, *Kokai Tokkyo Koho JP* 02235872, [*Chem. Abst.*, 1990, **114**, 122355]. b) A. Toshimitsu, C. Hirosawa, S. Tanimoto, S. Uemura, *Tetrahedron Lett.*, 1992, **33**, 4017.
13. M. Inoue, T. Sugita, Y. Kiso, K. Ichikawa, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1063.
14. M. Caron, K. B. Sharpless, *J. Am. Chem. Soc.*, 1985, **50**, 1557.
15. a) J. H. Billman, E. E. Parker, *J. Am. Chem. Soc.*, 1943, **65**, 2455. b) J. H. Billman, E. E. Parker, *J. Am. Chem. Soc.*, 1944, **66**, 1538.

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