A Facile Synthesis of Optically Pure Amines by Reduction of N-Acyl- α -methoxyalkylamines Derived from α -Amino Acids Using Triethylsilane

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Optically pure amines were synthesized effectively by Lewis acid-catalyzed triethylsilane reduction of N-acyl- α -methoxyalkylamines which were readily obtained by anodic oxidation of N-acyl- α -amino acids. This method was also applied to the conversion of an N-acyleptide into the corresponding optically pure amine derivative.

Keywords optically pure amine; triethylsilane; decarboxylation; α -amino acid; anodic oxidation; reduction; α -methoxyalkylamine

Optically active amines have recently attracted much attention as versatile building blocks¹⁾ and chiral auxiliaries.²⁾ Decarboxylation of α -amino acids having an asymmetric center in the side chain such as isoleucine and threonine and of peptides is a most straightforward method for the preparation of optically active amines. However, difficulty is frequently encountered in the decarboxylation of α -amino acids and peptides, for which drastic conditions are usually required.^{3,4)} Recently, effective methods for the decarboxylation of α -amino acids and their derivatives have been reported based on the photochemical reductive decarboxylation of N-protected α -amino acid N-hydroxypyridine-2-thione esters⁵⁾ and thermal decarboxylation of α -amino acids in the presence of cyclohexenone.⁶⁾

On the other hand, it is well known that anodic decarboxylation $^{7,8)}$ is quite effective for the conversion of N-acyl- α -amino acids into the N-acyl- α -methoxyalkylamines. Thus, for the synthesis of optically pure amines we require the reductive removal of the methoxyl group from N-acetyl- α -methoxyalkylamines. Recently, Shono $et\ al.^{9)}$ reported the successful preparation of 5-substituted N-acyl- α -methoxypiperidine α 0 using a large excess of NaBH4. However, an effective method for the reductive cleavage of α -acyl- α -methoxyalkylamines has not yet been reported.

We herein wish to report a facile synthesis of optically pure amines by Lewis acid-catalyzed triethylsilane (Et₃SiH) reduction^{11a,b)} of N-acyl- α -methoxyalkylamines, which were obtained by anodic oxidation of N-acyl- α -amino acids. The extension of this method to the decarboxylation of a peptide is also described.

Anodic oxidation of N-acetyl-L-isoleucine (1a) in MeOH containing a catalytic amount of NaOMe at 10-15 °C at a constant current with graphite electrodes gave (2R)-N-acetyl-1-methoxy-2-methylbutylamine (2a) in 96% yield (Chart 1). In a similar way, the other N-acyl- α -amino acids 1b—e were converted to the corresponding N-acyl- α -methoxyalkylamines 2b—e in almost quantitative yields. In addition, anodic oxidation of the peptide 1f resulted in the corresponding methoxylated compound 2f in 86% yield.

HN COOH MeOH HN OMe
$$\overline{\mathrm{BF}_3\mathrm{OEt}_2}$$
 HN COCH₃ 96% $\overline{\mathrm{COCH}_3}$ $2a$ $3a$ $Chart 1$

The results are shown in Table I. The electrolysis products 2a—f were obtained as mixtures of two diastereomers, ^{12,13)} and were used in the next step without further separation.

We next examined the Lewis acid-catalyzed EtaSiH reduction of the N-acyl-α-methoxyalkylamines obtained above. As a result, BF₃·OEt₂ was found to be a good catalyst for the reduction. Thus, the reduction of the methoxylated compound 2a was carried out by use of $Et_3SiH-BF_3 \cdot OEt_2$ at 5 °C (method A), affording (2R)-Nacetyl-2-methylbutylamine (3a) in 96% yield (Chart 1). Under similar conditions, 2b and 2f were converted to 3b and 3f in 84% and 89% yields, respectively. In the reduction of 2c, 2d, and 2e having acid-labile tert-butyldimethylsilyl (TBDMS) and tert-butoxycarbonyl(Boc) protecting groups, the reactions were carried out below -40 °C to give the desired products (method B). Trifluoroacetic acid (TFA)-Et₃SiH (method C)^{11b,14)} could also be employed for the reduction of 2b and 2f to afford 3b and 3f, respectively in satisfactory yields. However, in the case of 2c, desilylation occurred together with the formation of the desired reduction product 3c. These results are summarized in Table I.

The reduction of N-acyl- α -methoxyalkylamines described above presumably involves hydride transfer from silicon to the N-acyliminium ion and/or N-acylimine^{15,16)} which are formed under the Lewis acid-catalyzed conditions.

During the transformation, no epimerization took place at all at the asymmetric centers in the side chains; this was confirmed by the conversion of 3c and 3e into the known (2R)-(-)-hydroxypropylamine and (3R)-(-)-hydroxypyrrolidine, respectively. 6

This method involving anodic oxidation and Et_3SiH reduction will provide a useful approach for the synthesis of optically pure amines from N-acyl- α -amino acids and peptides.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-420 infrared spectrophotometer. $^1\mathrm{H-Nuclear}$ magnetic resonance ($^1\mathrm{H-NMR}$) spectra were taken at 200 MHz on a Bruker AC-200 spectrometer with tetramethylsilane (TMS) as an internal reference. Mass spectra (MS) were obtained with a Hitachi M-60 instrument. Optical rotations were measured by the use of a Perkin–Elmer model 243 polarimeter with a 1 cm³ capacity (10 cm path length) quartz cell. The electrolyses were carried out by the use of a Hokuto Potentio-Galvanostat (10 A—100 V) coupled to Hokuto HA-108A coulomb meter.

Starting Materials Compounds 1a—e were obtained from the corresponding α -amino acids by the usual methods.¹⁷⁾

A Typical Electrolysis Procedure A solution of 1a (20 mmol) in MeOH

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TABLE I. Anodic Oxidation of 1b—f and Et₃SiH Reduction of 2b—f

N-Acyl-α-amino acid	N-Acyl-α- methoxyalkylamine	Yield (%)	N-Acylamine	Method ^{a)}	Yield (%)
ZHN COOH	ZHN OMe	98	ZHN ZHN	A C	84 75
Th ^{b)} OTBDMS ZHN COOH	2b OTBDMS ZHN OMe	96	3b OR ZHN	B C	88 42 (3c) 51 (3c')
1c ^{b)} OCH ₂ Ph BocHN COOH	2c OCH₂Ph	98	3c (R = TBDMS) 3c' (R = H) OCH ₂ Ph	В	98
1d ^{b)}	BocHN OMe 2d TBDMSO	97	BocHN 3d	В	96
осн ₃	N OMe COCH ₃		TBDMSO, N COCH ₃ 3e		00
ZHN N COOH	ZHN N OMe	86	ZHN N Ph H	A C	89 87
1f .	2f		3f		

a) Method A, Et_3SiH – BF_3 · OEt_2 at 5 °C; method B, Et_3SiH – BF_3 · OEt_2 at -40 °C; method C, Et_3SiH –TFA at room temperature. b) Z=benzyloxycarbonyl; Boc = tert-butoxycarbonyl; TBDMS = tert-butyldimethylsilyl.

(30 ml) containing NaOMe (1 mmol) was electrolyzed at 5—10 °C using a 6.4 cm² of graphite anode–graphite cathode system in a non-divided cell. The electrolysis current was maintained at 0.6 A during the electrolysis. After the theoretical amount of electricity had passed, the electrolyzed solution was evaporated to dryness *in vacuo*. The residue was dissolved in EtOAc. The solution was washed with saturated aqueous NaHCO $_3$ solution and brine, dried (MgSO $_4$) and evaporated to dryness *in vacuo* to afford compound 2a.

(2*R*)-*N*-Acetyl-1-methoxy-2-methylbutylamine (2a) mp 36—37 °C. IR (Nujol): 3300 (NH), 1660 (CO) cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.91 (t, 3H, J=6.0 Hz, C₄-H), 0.93 (d, 3H, J=5.5 Hz, CH₃), 1.03—1.29 (m, 1H, C₃-H), 1.41—1.73 (m, 2H, C₂-H, C₃-H), 2.10 (s, 3H, COCH₃), 3.32 (s, 3H, OCH₃), 4.90—5.00 (m, 1H, C₁-H), 6.05 (br 1H, NH). MS m/z: 128 (M⁺ – CH₃O). *Anal.* Calcd for C₈H₁₇NO₂: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.46; H, 11.10; N, 8.69.

(2R)-N-Benzyloxycarbonyl-1-methoxy-2-methylbutylamine (2b) Colorless syrup. IR (film); 3320 (NH), 1705 (CO), 1520 cm $^{-1}$. 1 H-NMR (CDCl $_{3}$) δ : 0.88 (d, 3H, J=6.8 Hz, CH $_{3}$), 0.90 (t, 3H, J=6.6 Hz, C $_{4}$ -H), 1.00—1.30 (m, 1H, C $_{3}$ -H), 1.40—1.75 (m, 2H, C $_{3}$ -H, C $_{2}$ -H), 3.34 (s, 3H, OCH $_{3}$), 4.65—4.82 (m, 1H, C $_{1}$ -H), 4.99 (br, 1H, NH), 5.13 (s, 2H, PhCH $_{2}$ O), 7.34 (s, 5H, Ar-H). MS m/z: 219 (M $^{+}$ -CH $_{3}$ OH). Anal. Calcd for C $_{14}$ H $_{21}$ NO $_{3}$: C, 66.91; H, 8.42; N, 5.57. Found: C 66.72; H, 8.51; N, 5.45.

(2R)-N-Benzyloxycarbonyl-1-methoxy-2-(tert-butyldimethylsilyloxy)-propylamine (2c) Colorless syrup. IR (film): 3460 (NH), 3350, (NH), 1730 (CO), 1720 (CO), 1500 cm¹. ¹H-NMR (CDCl₃) δ : -0.06—0.05 (m, 6H, SiCH₃), 0.81—0.84 (m, 9H, tert-Bu), 1.04, 1.11 (each d, 3H, J=6.4 Hz, C₃-H), 3.29, 3.33 (each s, 3H, OCH₃), 3.80—3.95 (m, 1H, C₂-H), 4.61, 4.71 (each dd, 1H, J=1.8, 9.9 Hz, C₁-H), 5.09 (s, 2H, PhC $\underline{\text{H}}_2$ O), 5.42 (d, 1H, J=9.9 Hz, NH), 7.25—7.36 (m, 5H, Ar-H). MS m/z: 321 (M⁺ - CH₃OH). Anal. Calcd for C₁₈H₃₁NO₄Si: C, 61.15; H, 8.84; N, 3.96; Si, 7.94. Found: C, 60.98; H, 9.27; N, 3.96; Si, 8.05.

(2R)-N-tert-Butyloxycaronyl-1-methoxy-2-benzyloxypropylamine (2d) Colorless syrup. IR (film): 3450 (NH), 3320, 1725 (CO), 1500 cm $^{-1}$, 1 H-NMR (CDCl $_{3}$) δ : 1.14, 1.23 (each d, 3H, J=6.5 Hz, C_{3} -H), 1.44, 1.46 (each s, 9H, tert-Bu), 3.37, 3.38 (each s, 3H, OCH $_{3}$), 3.49—3.62, 3.65—3.82

(each m, 1H, C₂-H), 4.40—4.85 (m, 3H, C₁-H, OCH₂), 5.20, 5.35 (each br, 1H, NH), 7.25—7.35 (m, 5H, Ar-H). MS m/z: 263 (M $^+$ – CH₃OH). Anal. Calcd for C₁₆H₂₅NO₄: C, 65.06; H, 8.53; N, 4.74. Found: C, 64.81; H, 8.35; N, 4.41.

(4R)-1-Acetyl-2-methoxy-4-(tert-butyldimethylsilyloxy)-pyrrolidine (2e) Colorless syrup. IR (film): 3450 (NH), 1665 (CO), 1415 cm⁻¹.

¹H-NMR (CDCl₃) δ: 0.07 (s, 6H, SiCH₃), 0.88 (s, 9H, tert-Bu), 1.75—2.10, 2.15—2.39 (each m, 2H, C₃-H), 2.07, 2.13, 2.14 (each s, 3H, COCH₃), 3.27, 3.29, 3.37, 3.40 (each s, 3H, OCH₃), 3.10—3.55, 3.65—3.95 (each m, 2H, C₅-H), 4.30—4.50, 4.50—4.75 (each m, 1H, C₄-H), 5.00—5.45 (m, 1H, C₂-H). MS m/z: 242 (M⁺ – CH₃O). Anal. Calcd for C₁₃H₂₇NO₃Si: C, 57.10; H, 9.95; N, 5.12; Si, 10.27. Found: C, 56.84; H, 9.75; N, 4.78; Si, 9.82.

N-Benzyloxycarbonyl-L-phenylalanine *N*-(1-Methoxy-2(*R*)-methyl)butyl Aimde (2f) mp 138—139 °C (MeOH). IR (Nujol): 3300 (NH), 1690 (CO), 1660 (CO), 1540 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.66 (d, 3H, J=6.8 Hz, CH₃), 0.80—0.90 (m, 3H, CH₂CH₃), 0.85—1.60 (m, 3H, CHCH₂), 3.11 (s, 3H, OCH₃), 2.90—3.10 (m, 2H, CH₂ph), 4.45 (q, 1H, J=7.0 Hz, NHCHCO), 4.80—5.00 (m, 1H, NHCHO), 5.05, 5.13 (ABq, 2H, J=12.3 Hz, PhCH₂O), 5.43 (m, 1H, NH), 5.90—6.10 (m, 1H, NH), 7.00—7.35 (m, 5H, Ar-H), 7.33 (s, 5H, Ar-H). MS m/z: 366 (M⁺ - CH₃OH). *Anal*. Calcd for C₂₃H₃₀N₂O₄: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.42; H, 7.70; N, 7.01.

Typical Procedures for Et₃SiH Reduction Method A: A solution of **2a** (2 mmol) and Et₃SiH (2.4 mmol) in dry CH_2Cl_2 (3 ml) was treated with BF₃OEt₂ (2.4 mmol) at 5 °C. After being stirred at 5 °C for 2 h, the reaction mixture was diluted with CHCl₃. The solution was washed with saturated aqueous NaHCO₃ solution and brine. The organic layer was dried (MgSO₄) and concentrated to dryness *in vacuo*, and the resulting syrup was subjected to silica gel chromatography (CHCl₃–acetone, 5:1) to afford compound **3a**.

Method B: A solution of 2c (2 mmol) and Et_3SiH (4 mmol) in dry CH_2Cl_2 (3 ml) was treated with BF_3OEt_2 (4 mmol) at -40 °C. The temperature of the solution was maintained at -40 °C until the starting material disappeared on thin layer chromatography (TLC) (1—2 h). The reaction mixture was diluted with $CHCl_3$. The solution was washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried (MgSO₄) and evaporated to dryness *in vacuo*. Purification of the

residue by silica gel chromatography (n-hexane-EtOAc, 10:1) gave compound 3c.

Method C: A solution of **2b** (2 mmol) and Et_3SiH (2.4 mmol) in dry CH_2Cl_2 (3 ml) was treated with TFA (6 mmol) at 5°C. The reaction mixture was stirred at room temperature for 2 h, then quenched by addition of saturated aqueous NaHCO₃ solution. The mixture was extracted with CHCl₃. The organic layer was separated, dried (MgSO₄) and then evaporated to dryness *in vacuo* to give a syrup, which was purified by silica gel chromatography (n-hexane–EtOAc, 10:1) to afford compound **3b**.

(2R)-N-Acetyl-2-methylbutylamine (3a) This compound was prepared by method A. Colorless syrup, $[\alpha]_D^{2^2.5} + 5.23^{\circ}$ (c = 1.11, CHCl₃). IR (film): 3300 (NH), 1655 (CO) cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.87—0.94 (m, 6H, C₄-H, CH₃), 1.04—1.26 (m, 1H, C₃-H), 1.30—1.67 (m, 2H, C₂-H, C₃-H), 1.99 (s, 3H, COCH₃), 2.99—3.26 (m, 2H, C₁-H), 5.61 (br, 1H, NH). MS m/z: 129 (M⁺). Anal. Calcd for C₇H₁₅NO: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.92; H, 12.08; N, 10.61.

(2*R*)-*N*-Benzyloxycarbonyl-2-methylbutylamine (3b) This compound was obtained by both method A and method C. Colorless syrup, $[\alpha]_{2}^{25.5} + 4.07^{\circ}$ (c=1.13, CHCl₃). IR (film): 3330 (NH), 1710 (CO), 1540 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.89 (d, 3H, J=6.6 Hz, CH₃), 0.90 (t, 3H, J=7.2 Hz, C₄-H), 1.00—1.63 (m, 3H, C₂-H, C₃-H), 2.90–3.23 (m, 2H, C₁-H), 4.77 (br, 1H, NH), 5.10 (s, 2H, PhCH₂O), 7.33 (s, 5H, Ar-H). MS m/z. 221 (M⁺). Anal. Calcd for C₁₃H₁₉NO₂: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.41; H, 9.07; N, 6.36.

(2R)-N-Benzyloxycarbonyl-2-(tert-butyldimethylsilyloxy)propylamine (3c) This compound was prepared by both method B and method C. Colorless syrup, $[\alpha]_D^{25.5} - 22.1^\circ$ (c = 1.26, CHCl₃). IR (film): 3470 (NH), 3350 (NH), 1730 (CO), 1710 (CO) cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.01 (s, 6H, SiCH₃), 0.85 (s, 9H, tert-Bu), 1.07 (d, 3H, J = 6.2 Hz, C₃-H), 2.91—3.05 (m, 1H, C₁-H), 3.18—3.31 (m, 1H, C₁-H), 3.83—3.92 (m, 1H, C₂-H), 4.96 (br, 1H, NH), 5.06 (s, 2H, PhCH₂O), 7.21—7.34 (m, 5H, Ar-H). MS m/z: 323 (M⁺). Anal. Calcd for C₁₇H₂₉NO₃Si: C, 63.12; H, 9.04; N, 4.33; Si, 8.68. Found: C, 62.88; H, 8.90; N, 4.10; Si, 8.32.

(2*R*)-*N*-Benzyloxycarbonyl-2-hydroxypropylamine (3c') This compound was formed as a by-product in the reduction of 3c using method C. Colorless syrup, $[\alpha]_D^{25.5} - 20.3^\circ$ (c = 1.19, CHCl₃). IR (film): 3350 (NH), 2910 (OH), 1700 (CO) cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.18 (d, 3H, J = 6.3 Hz, CH₃), 2.04 (br, 1H, OH), 2.98—3.12 (m, 1H, C₁-H), 3.28—3.40 (m, 1H, C₁-H), 3.91 (m, 1H, C₂-H), 5.11 (s, 2H, PhCH₂O), 5.21 (br, 1H, NH), 7.26—7.37 (m, 5H, Ar-H). MS m/z: 209 (M⁺). Anal. Calcd for C₁₁H₁₅NO₃: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.83; H, 7.25; N, 6.49.

(2*R*)-*N-tert*-Butyloxycarbonyl-2-benzyloxypropylamine (3d) This compound was prepared by method B. Colorless syrup, $[\alpha]_D^{26} - 37.9^\circ$ (c = 1.22, CHCl₃). IR (film): 3450 (NH), 3350, 1720 (CO), 1500 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.19 (d, 3H, J = 6.2 Hz, C_3 -H), 1.44 (s, 9H, tert-Bu), 3.00—3.13 (m, 1H, C_1 -H), 3.20—3.40 (m, 1H, C_1 -H), 3.58—3.66 (m, 1H, C_2 -H), 4.45, 4.61 (ABq, 2H, J = 11.7 Hz, PhCH₂O), 4.86 (br, 1H, NH), 7.26—7.36 (m, 5H, Ar-H). MS m/z: 264 (M⁺). *Anal.* Calcd for C_{15} H₂₃NO₃: C, 67.90: H, 8.74; N, 5.28. Found: C, 67.71; H, 8.65; N, 5.06.

(3R)-N-Acetyl-3-(tert-butyldimethylsilyloxy)propylamine (3e) This compound was prepared by method B. Colorless syrup, $[\alpha]_b^{24.5} - 23.4^\circ$ (c=1.22, CHCl₃); IR (film): 3350 (NH), 1650 (CO) cm⁻¹ ¹H-NMR (CDCl₃) δ: 0.01 (s, 6H, SiCH₃), 0.80 (s, 9H, tert-Bu), 1.60—2.10 (m, 2H, C₄-H), 1.95, 1.98 (each s, 3H, CH₃), 3.10—3.80 (m, 4H, C₂-H, C₅-H), 4.25—4.58 (m, 1H, C₃-H). MS m/z: 228 (M⁺ - CH₃). Anal. Calcd for C₁₂H₂₅NO₂Si: C, 59.21; H, 10.35; N, 5.75; Si, 11.54. Found: C, 58.85; H, 10.38; N, 5.80; Si, 11.18.

N-Benzyloxycarbonyl-L-phenylalanine *N*-(2(*R*)-Methylbutyl)amide (3f) Both method A and method C were applied to obtain this compound. mp 133—134 °C (MeOH), $[\alpha]_{\rm p}^{25.5}$ + 5.49° (c = 1.02, CHCl₃). IR (Nujol): 3300 (NH), 1690 (CO), 1655 (CO); 1530 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.72 (d, 3H, J = 6.7 Hz, CHCH₃), 0.81 (3H, t, J = 7.3 Hz, CH₂CH₃), 0.85—1.50 (m, 3H, CHCH₂CH₃), 2.85—3.18 (m, 4H, CH₂Ph, NHCH₂-), 4.29—4.41 (m, 1H, NHCH₂CO), 5.08 (s, 2H, PhCH₂O), 5.45 (br, 1H, NH), 5.70 (br, 1H, NH), 7.17—7.37 (m, 10H, Ar-H). MS m/z: 366 (M + -H₂). Anal. Calcd for C₂₂H₂₈N₂O₃: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.46; H, 7.75; N, 7.48.

Conversion of 3c to 2(R)-(-)-Hydroxypropylamine Hydrochloride Compound 3c (835 mg, 2.68 mmol) was dissolved in MeOH (30 ml) and the solution was subjected to hydrogenolysis over 10% Pd-C (0.1 g) at atmospheric pressure. After a theoretical amount of hydrogen had been absorbed, the catalyst was filtered off and the filtrate was evaporated to dryness in vacuo. The resulting syrup was dissolved in 22% HCl in MeOH (1 ml) and the solvent was removed under reduced pressure. The resulting

crystals were triturated with ether to give colorless needles (190 mg, 63%), mp 111—113 °C (lit. 6) 113 °C, $[\alpha]_D^{25.5}$ – 32.5° (c = 2.74, H₂O) (lit. 6) $[\alpha]_D^{20}$ – 32.4° (c = 1.46, H₂O)). IR (film): 3350 (NH), 2850, 1960, 1600 cm $^{-1}$. 1 H-NMR (D₂O) δ : 1.24 (d, 3H, J = 6.4 Hz, CH₃), 2.88 (dd, 1H, J = 9.0, 13.1 Hz, C₁-H), 3.10 (dd, 1H, J = 3.4, 13.1 Hz, C₁-H), 3.95—4.12 (m, 1H, C₂-H). MS m/z: 76 (M $^+$).

Conversion of 3e to (3R)-(-)-Hydroxypyrrolidine Hydrochloride A mixture of compound 3e (1.26 g, 5.18 mmol) and 6 n HCl (5 ml) was refluxed for 6 h. After cooling, the reaction mixture was diluted with H₂O (5 ml), and the solution was washed with EtOAc. The aqueous layer was concentrated to dryness *in vacuo*. The crystalline residue was triturated with ether to give pale brown needles (550 mg, 85%). An analytical sample was prepared by recrystallization from EtOH-ether (1:1), mp 107—108 °C (lit. 61 109 °C), $[\alpha]_{D}^{26} - 9.20^{\circ}$ (c = 1.74, MeOH) (lit. 61 [α] $_{D}^{20} - 7.60^{\circ}$ (c = 3.45, MeOH)). IR (Nujol): 3400 (NH), 1620, 1450 cm⁻¹. 11 H-NMR (D₂O) δ : 2.02—2.25 (m, 2H, C₄-H), 3.26—3.55 (m, 4H, C₂-H, C₅-H), 4.61—4.68 (m, 1H, C₃-H). MS m/z: 87 (M⁺).

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References and Notes

- T. Miyadera, Y. Sugimura, T. Hashimoto, T. Tanaka, K. Iino, T. Shibata, and S. Sugiura, J. Antibiot., 36, 1034 (1983).
- 2) J. W. ApSimon and T. L. Collier, Tetrahedron, 42, 5157 (1986).
- 3) G. Hilgetag and A. Martini, "Preparative Organic Chemistry," John Wiley and Sons, New York, 1972, p. 1003.
- 4) H. Henecka, "Methoden der Organischen Chemie," 4th ed., Vol. VIII, ed. by E. Müller, Georg Thieme Verlag, Stuttgart, 1952, p. 489.
- D. H. R. Barton, Y. Hérve, P. Potier, and J. Thierry, J. Chem. Soc., Chem. Commun., 1984, 1298.
- M. Hashimoto, Y. Eda, Y. Osanai, T. Iwai, and S. Aoki, Chem. Lett., 1986, 893.
- T. Iwasaki, H. Horikawa, K. Matsumoto, and M. Miyoshi, Tetrahedron Lett., 1976, 191; idem, Bull. Chem. Soc. Jpn., 52, 826 (1979); T. Nishitani, H. Horikawa, T. Iwasaki, K. Matsumoto, I. Inoue, and M. Miyoshi, J. Org. Chem., 47, 1706 (1982).
- R. P. Linstead, B. R. Shephard, and B. C. L. Weedon, J. Chem. Soc., 1951, 2854.
- T. Shono, Y. Matsumura, K. Tsubata, and K. Uchida, J. Org. Chem., 51, 2590 (1986).
- 10) The reductive removal of the methoxyl group from 5-substituted N-acyl-2-methoxypiperidine was also achieved by thermal elimination of methanol, followed by hydrogenation of the resulting enamine over palladium on charcoal. See, K. Irie, K. Aoe, T. Tanaka, and S. Saito, J. Chem. Soc., Chem. Commun., 1985, 633.
- a) An example for the reductive cleavage of an N,O-acetal using Et₃SiH-BF₃·OEt₂ has recently been reported. See, M. E. Maier and K. Evertz, *Tetrahedron Lett.*, 29, 1677 (1988); b) For the reductive cleavage of acetals using Et₃SiH-TFA, see D. N. Kursanov, Z. N. Parnes, and N. M. Loim, *Synthesis*, 1974, 633.
- 12) In any case, the ratio of the diastereomers was observed to be approximately 2:1 from the NMR spectra.
- 13) Seebach et al. obtained a 1:1-mixture of the diastereomers in the electrolysis of an N-methoxycarbonyl-O-tert-butyldimethylsilyl-L-threonine. See, P. Renaud and D. Seebach, Angew. Chem. Int. Ed. Engl., 25, 843 (1986); D. Seebach, R. Charczuk, C. Gerber, and P. Renaud, Helv. Chim. Acta, 72, 401, (1989).
- 14) The conversion of N-acylhydroxymethylamines to the corresponding N-acylmethylamines using Et₃SiH-TFA has been claimed by Weinreb et al. See, J. Auerbach, M. Zamore, S. M. Weinreb, J. Org. Chem., 41, 725 (1976).
- 15) The reduction of alkylimines to the corresponding alkylamines by use of Et₃SiH in the presence of TFA has been achieved by Hiyama et al. See, M. Fujita and T. Hiyama, J. Org. Chem., 53, 5415 (1988).
- T. Iwasaki, H. Horikawa, K. Matsumoto, and M. Miyoshi, J. Org. Chem., 42, 2419 (1977).
- S. Sakakibara and M. Fujino, Bull. Chem. Soc. Jpn., 39, 947 (1966);
 N. Kurokawa and Y. Ohfune, J. Am. Chem. Soc., 108, 6043 (1986);
 T. Mizoguchi, G. Levin, D. W. Wooley, and J. M. Stewart, J. Org. Chem., 33, 903 (1968);
 F. Chillemi, Gazz. Chim. Ital., 93, 1079 (1963).