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Synthetic Study of *cis*-3-Amino-4-(1-hydroxyalkyl)azetidin-2-ones Using L-Aspartic Acid as a Chiral Synthon

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The stereoselective synthesis of *cis*-3-amino-4-(1-hydroxyalkyl)azetidin-2-ones from L-aspartic acid is described. The thermodynamically less stable isomers with 3,4-*cis* stereochemistry, key intermediates for the synthesis of various substituted monobactams, were obtained by hydrogenation of the 3-oxyimino-azetidin-2-ones prepared from azetidin-2-ones and isoamyl nitrite. Furthermore, some simple analogues of monobactams were synthesized.

Keywords——monobactam; L-aspartic acid; 3-oxyimino-azetidin-2-one; 3-aminoazetidin-2-one

Monobactams[1] are a new class of β-lactam antibiotics discovered independently by two groups at Takeda[2] and Squibb[3] in 1981. Since monobactams are structurally simple and also are considered to be more stable chemically than other important non-classical β-lactam antibiotics such as carbapenems,[4] chemical modifications at the C_3 amido side chain and C_4 substituents have been extensively carried out recently. We became interested in (3*S*,4*S*)-3-amino-4-(1-hydroxyalkyl)azetidin-2-ones **1** or their equivalents as key intermediates for various 3,4-*cis*-substituted monobactams, because it was considered that the antimicrobial activity of 3,4-*cis* isomers would be higher than that of the corresponding 3,4-*trans* isomers.[5] However, the 3,4-*cis* stereochemistry is less easily accessible than the 3,4-*trans* stereochemistry. The racemic 3,4-*cis*-3-acylamino-4-substituted azetidin-2-ones have already been prepared by cycloaddition of ketenes and Schiff bases,[6] and resolution of the racemates has also been carried out by the Takeda group.[5] In this paper we describe the preparation of **12** and **30** from L-aspartic acid, as well as the preparation of some analogues of monobactams.

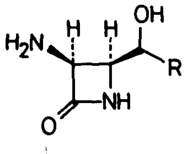

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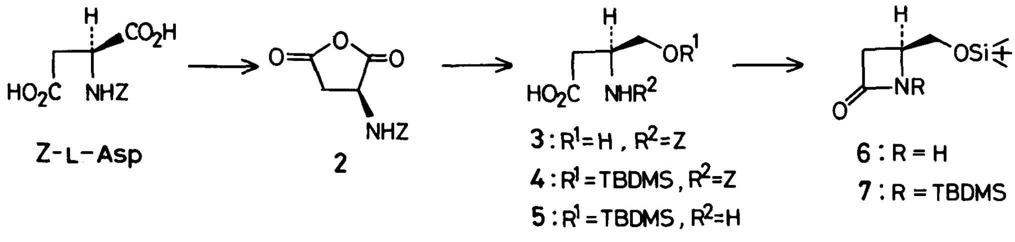
Chart 1

In the previous papers,[7] we showed that *cis*-carbapenems can be stereoselectively elaborated by introducing the C_6-side chain (carbapenem numbering) into the γ- or δ-lactone followed by recyclization into the corresponding β-lactams. However, the same strategy could not be applied to the 3,4-*cis* substituted 3-amino β-lactams due to the lack of stereoselectivity. The synthesis of 4-substituted β-lactams has been well investigated in connection with the synthesis of carbapenem antibiotics.[4] Therefore, the most straightforward route seemed to involve the introduction of a nitrogen substituent with a *cis* relationship at the 3-position of the (4*S*)-4-hydroxymethyl-azetidin-2-one derivative **7**, now available from L-aspartic acid. The Merck group reported the preparation of (4*S*)-4-hydroxymethyl-azetidin-2-one by Grignard reagent-mediated cyclization of *N*-trimethylsilylated aspartic acid dibenzyl ester followed by reduction[8] of the methoxycarbonyl group at C-4. As an alternative, **7** could also be obtained from L-aspartic acid as shown in Chart 2. *N*-Benzyloxycarbonylaspartic acid anhydride **2** was prepared and reduced with sodium borohydride in the same manner as described in the previous paper.[7a] Simple extractive work-up after acidification of the reduction mixture gave the uncyclized hydroxy acid **3** instead of the γ-lactone. The protection of the γ-hydroxyl group with *tert*-butyldimethylsilyl and the deprotection of the Z group afforded the β-amino acid **5** in quantitative yield from **3** (3 steps). The β-lactam ring formation was carried out by our procedure[9] (Ph_3P–PySSPy–CH_3CN) in 74% yield to afford the azetidin-2-one **6**. The amide proton was further protected with a *tert*-butyldimethylsilyl group to give the azetidin-2-one **7** in 40% overall yield from *Z*-aspartic acid. Shibuya and his co-workers have reported that the reaction of the lithium enolate of **7** with 2,4,6-tri-isopropylbenzenesulfonyl azide afforded the *trans* substituted azido azetidin-2-one exclusively.[10] Therefore, the *trans* derivative (3*S*,4*R*-) could be formed stereoselectively from the (4*R*)-4-hydroxymethyl-azetidin-2-one derivative obtained from D-aspartic acid or L-malic acid.[10]



TBDMS = *tert*-butyldimethylsilyl

Chart 2

We thought that the hydrogenation of the keto oxime **8** would occur from the less hindered α-side (opposite to the C_4-substituent) to afford the required 3,4-*cis* azetidin-2-one predominantly. Thus, the lithium enolate of **7** was prepared from **7** and lithium diisopropylamide, and was reacted with isoamyl nitrite[11] in tetrahydrofuran (THF) at −78 °C to give the α-keto oxime **8** in 63% yield as a *syn–anti* mixture. Hydrogenation was examined with the mixture using PtO_2, Pd–C, or Rh_2O_3 as catalysts in various solvents. Among them, PtO_2 in ethyl acetate gave the most satisfactory result. Thus, the *syn–anti* mixture of the α-keto oxime **8** in ethyl acetate was stirred under a hydrogen atmosphere in the presence of PtO_2 to give the desired *cis*-amino azetidin-2-one **9** and *trans* isomer **10** in 72% and 10% yields, respectively. The stereochemistry was determined by proton nuclear magnetic resonance (^{1}H-NMR). The coupling constant of $J_{3,4} = 5.8$ Hz in the major isomer and that of 2.7 Hz in the minor isomer

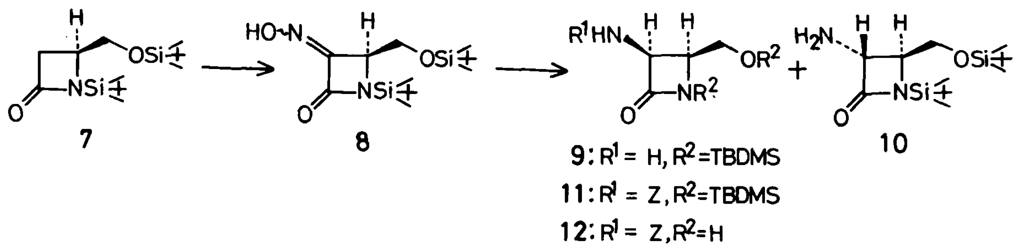


Chart 3

clearly supported the assigned stereochemistry. The amino group of the relatively unstable **9** was protected with a benzyloxycarbonyl group to give the stable azetidin-2-one **11**, which is considered to be a useful intermediate for a variety of 4-substituted monobactams (Chart 3). Ether and acyl derivatives could be readily prepared by utilizing the hydroxyl group as a nucleophile. By conversion of the hydroxyl group into a leaving group, another hetero atom could also be introduced.

Other attractive intermediates are 4-hydroxyethyl derivatives, since it is hoped that the introduction of a methyl group might offer increased stability to β-lactamase.[12] Our initial plan was to oxidize **12** to the aldehyde, followed by reaction with alkyl metals such as methyllithium or methylmagnesium halide. However, all attempts to obtain the aldehyde from **12** were unsuccessful. The only example of the oxidation reaction which proceeded smoothly was the carboxylic acid formation (Chart 4). Jones oxidation of the alcohol **12** followed by treatment with ethereal diazomethane afforded the 4-methoxycarbonyl derivative **13** in optically active form (70% yield). As mentioned above, the racemate of **13** was stereoselectively prepared by the reaction of the appropriate ketene and Schiff base.[6]

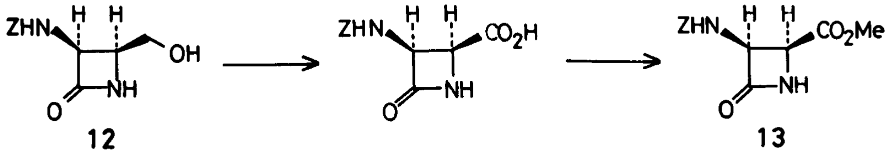


Chart 4

In order to obtain the aldehyde, oxidation of the alcohol prior to the introduction of 3-amino substituents was attempted (Chart 5). Thus, **6** was converted into the p-methoxybenzyl derivative **14** with p-methoxybenzyl chloride and silver oxide in acetonitrile, and the crude **14** was treated with 1 N HCl in methanol to afford the alcohol **15** in 89% yield (two steps). The oxidation of the alcohol **15** to the aldehyde **16** proceeded very smoothly with dimethyl sulfoxide (DMSO)–oxalyl chloride–Et$_3$N (Swern oxidation) in methylene chloride. The resulting aldehyde **16**, without purification, was treated with excess methylmagnesium bromide in ether to afford the 4-hydroxyethyl derivative **17*S*** and **17*R*** in 45% and 32% yields, respectively, from **15**. The absolute configuration of the newly formed chiral center was determined by comparison with an authentic sample prepared from L-threonine as shown in Chart 6. *N*-Benzyloxy-carbonyl-*O*-*tert*-butyldimethylsilyl derivative **20** was prepared from L-threonine, and was subjected to Arndt–Eistert reaction to form the homologated methyl ester **22**. The conventional protection–deprotection procedure afforded the p-methoxybenzylated β-amino acid **25**, which was then cyclized by the Ph$_3$P–PySSPy–CH$_3$CN method[9] to give the β-lactam **26** in 77% yield. The deprotection of the *tert*-butyldimethylsilyl group gave the stereochemically established β-lactam **27**. By comparison with **27** (^{1}H-NMR, infrared (IR) spectra, optical rotation and thin layer chromatographic behavior), the less polar isomer **17*S***

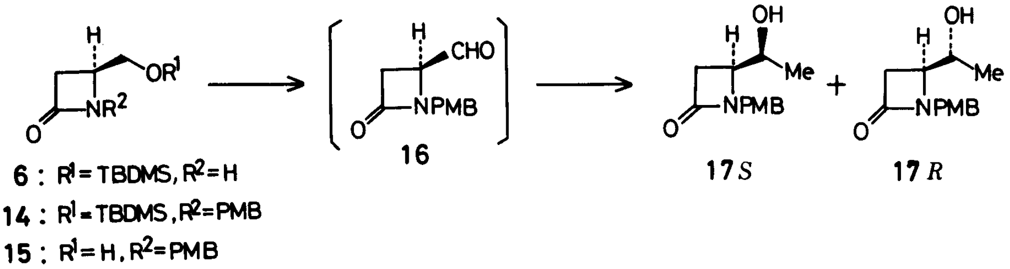


Chart 5

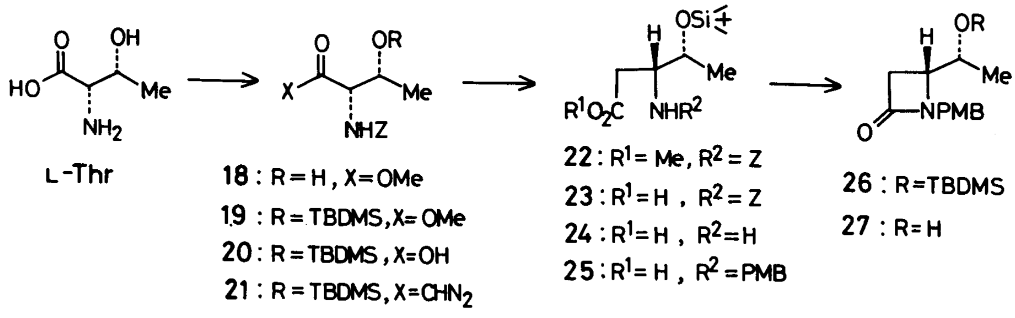


Chart 6

was found to be the enantiomer of **27**. Thus, the newly formed chiral centers in **17*S*** and **17*R*** were unambiguously established as *S* and *R*, respectively.

We also planned to synthesize the methoxy derivatives as simple analogues of monobactams (Chart 7). The less polar isomer **17*S*** was methylated with methyl iodide and sodium hydride to give the methoxy derivative **28*S***. Protection with other groups and generation of the free hydroxyl group after introduction of the benzyloxycarbonylamino group should also be possible. At first **28*S*** was treated with lithium diisopropylamine (LDA) and isoamyl nitrite in the same manner as in the case of **7**, but no α-keto oxime was obtained. After a number of experiments with various bases, solvents and temperatures, the desired keto oxime **29*S*** was obtained in 49% yield by lithiation with lithium hexamethyldisilazide followed by reaction with isoamyl nitrite. Even in the presence of excess base, the starting β-lactam **28*S*** was recovered in 43% yield. The reduction of the oxime **29*S*** was carried out in the same manner as used in the case of **8**. In this case, the stereoselectivity was not very high (*cis*/*trans*), and the *cis* amine **30*S*** and *trans* amine **31*S*** were isolated in 59% and 19% yields, respectively (*cis*/*trans*=3). The free amino group was protected with benzyl chloroformate–$NaHCO_3$ to afford the Z-amino derivative **32*S*** in a high yield, and the *p*-methoxybenzyl group attached to the β-lactam nitrogen was removed in 67% yield with potassium persulfate. The 2,4-dimethoxybenzyl group has frequently been employed for the protection of the β-lactam nitrogen. However, the present result shows that the rather expensive 2,4-dimethoxybenzyl group could be replaced by a *p*-methoxybenzyl group (PMB). Furthermore, two methods of protection are possible for the PMB derivative; direct alkylation and the reduction of the Schiff base. Similar deprotection of the PMB group was recently reported by Shiozaki and his co-workers.[13] From **33*S***, the monobactam analogue **36*S*** was prepared according to the known procedure.[6,14]

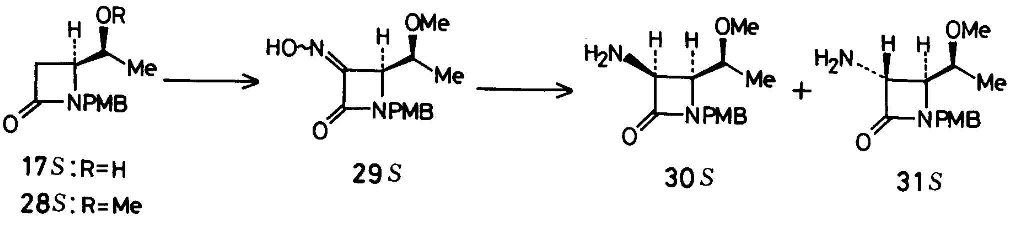
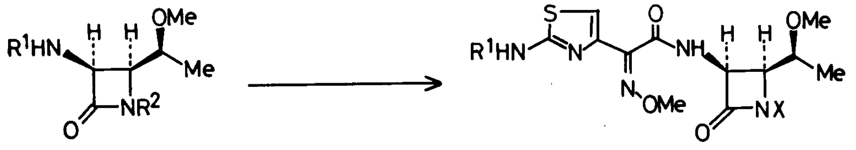


Chart 7

By means of the same reaction sequences, isomeric **36*R*** was also synthesized from the *R*-isomer **17*R***. In this series, the isomeric α-keto oxime (*syn*–*anti*) could be separated by silica gel column chromatography (but the stereochemistry of these isomers could not be determined), and each isomer was reduced. Both isomers showed higher stereoselectivity (*cis*/*trans* ratio ranging between 9—14) compared to the *S*-isomer.

In conclusion, the present investigation offers a new methodology for the enantioselective



32 *S* : R^1= Z, R^2=PMB
33 *S* : R^1= Z, R^2=H

34 *S* : R^1= $ClCH_2CO$, R^2=H
35 *S* : R^1 = $ClCH_2CO$, R^2=SO_3Na
36 *S* : R^1= H, R^2 =SO_3Na

Chart 8

preparation of 3-aminoazetidin-2-ones with the thermodynamically less stable 3,4-*cis* relationship. Furthermore, the resulting aminoazetidin-2-ones are considered to be potential intermediates for the synthesis of various substituted monobactam analogues.

Experimental

Melting points were measured on a Yamato MP-21 apparatus and are uncorrected. ^{1}H-NMR spectra were obtained on a JEOL FX-100 spectrometer and chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS). Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. IR spectra were measured on a JASCO A-102 spectrometer. Mass spectra (MS) were measured with a JEOL JMS-01 SG-2 mass spectrometer. Optical rotations were measured with a JASCO DIP-140 digital polarimeter. Silica gel (Wakogel C-200 or C-300) was used for column chromatography and silica gel (Kiesel gel 60 F_{254}, Merck) for analytical thin layer chromatography.

(3*S*)-3-Benzyloxycarbonylamino-4-hydroxybutanoic Acid (3)——*N*-Benzyloxycarbonyl L-aspartic acid anhydride **2** (4.94 g, 20 mmol) in THF (16 ml) was added dropwise to a suspension of $NaBH_4$ (757 mg, 20 mmol) in THF (4 ml) at 0°C. The reaction mixture was stirred at room temperature for 1 h. Saturated NaCl (2 ml) and 2 N HCl (2 ml) were added to the reaction mixture and the product was extracted with ethyl acetate. The organic solution was washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was triturated with methylene chloride to give **3** (2.96 g, 59%). mp 109—110 °C, $[\alpha]_D^{20}$ -10.6° ($c=1.0$, MeOH). MS *m/e*: 253 (M^+). IR (Nujol): 3400—2600, 3300, 1685 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.46 (1H, dd, $J=16.0$, 7.4 Hz), 2.66 (1H, dd, $J=16.0$, 6.2 Hz), 3.53 (1H, dd, $J=11.8$, 6.4 Hz), 3.65 (1H, dd, $J=11.8$, 5.4 Hz), 4.07 (1H, m), 5.10 (2H, s), 7.36 (5H, s).

(3*S*)-3-Amino-4-(*tert*-butyldimethylsilyloxy)butanoic Acid (5)——A mixture of the hydroxy acid **3** (506 mg, 2.0 mmol), *tert*-butyldimethylsilyl chloride (725 mg, 4.8 mmol) and imidazole (681 mg, 10 mmol) in dimethylformamide (DMF 8 ml) was stirred at room temperature overnight. Ether was added, and the organic solution was washed successively with cold 1 N HCl, cold water and saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude disilylated product, which was used for the next reaction without further purification. It was dissolved in THF (18 ml), 0.5 N HCl (2 ml) was added at 0 °C, and the reaction mixture was stirred at 0 °C for 25 min. Cold water was added and the product was extracted with ethyl acetate. The organic solution was washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was applied to a pad of silica gel to remove polar materials (eluted with ethyl acetate). The solvent was removed under reduced pressure, and the resulting carboxylic acid **4** was used for the next reaction without further purification. The crude carboxylic acid **4** in MeOH (10 ml) was stirred under a hydrogen atmosphere in the presence of 5% Pd–C for 2 h. The catalyst was filtered off on a celite pad, and removal of the solvent under reduced pressure gave the β-amino acid **5** (466 mg, quantitative yield from **3**). $[\alpha]_D^{20}$ -13.6° ($c=1.0$, MeOH). MS *m/e*: 234 ($M^+ + 1$). IR (Nujol): 3200—2300, 1590 cm^{-1}. ^{1}H-NMR (CD_3OD–$CDCl_3$) δ: 0.15 (6H, s), 0.95 (9H, s), 2.3—2.6 (2H, m), 3.3—3.6 (1H, m), 3.65—3.9 (2H, m).

(4*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)azetidin-2-one (6)——Triphenylphosphine (315 mg, 1.2 mmol) in acetonitrile (6 ml) was slowly added to a solution of the β-amino acid **5** (233 mg, 1.0 mmol) and 2,2′-dipyridyl disulfide (264 mg, 1.2 mmol) in acetonitrile (44 ml) under heating at 80 °C over a period of 30 min. The reaction mixture was heated for another 1.5 h at that temperature. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with Et_2O: hexane = 2 : 1) to give the β-lactam **6** (160 mg, 74%). $[\alpha]_D^{20}$ $+31.2$° ($c=1.93$, $CHCl_3$). MS *m/e*: 200 ($M^+ - CH_3$). IR (KBr): 3200, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.90 (9H, s), 2.63 (1H, m), 2.99 (1H, m), 3.48—3.87 (2H, m), 6.00 (1H, br s).

(4*S*)-1-(*tert*-Butyldimethylsilyl)-4-(*tert*-butyldimethylsilyloxymethyl)azetidin-2-one (7)——A mixture of the β-lactam **6** (660 mg, 3.07 mmol), triethylamine (0.51 ml, 3.67 mmol) and *tert*-butyldimethylsilyl chloride (556 mg, 3.70 mmol) in DMF (5 ml) was stirred at room temperature overnight. The reaction mixture was poured into ice water, and the product was extracted with ether. The organic solution was washed with saturated NaCl and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with Et_2O: hexane = 1 : 2) to give **7** (1.00 g, 99%). $[\alpha]_D^{20}$ $-29.4°$ (c = 1.11, $CHCl_3$). MS *m/e*: 329 (M^+), 314 ($M^+ - CH_3$). IR ($CHCl_3$): 2950, 1730 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.23 (3H, s), 0.24 (3H, s), 0.90 (9H, s), 0.96 (9H, s), 2.75 (1H, dd, J = 15.4, 2.5 Hz), 3.07 (1H, dd, J = 15.4, 4.8 Hz), 3.50—3.80 (3H, m).

(4*S*)-1-(*tert*-Butyldimethylsilyl)-3-hydroxyimino-4-(*tert*-butyldimethylsilyloxymethyl)azetidin-2-one (8)——The β-lactam **7** (76.6 mg, 0.232 mmol) in THF (0.5 ml) was added to a THF solution (1.5 ml) of lithium diisopropylamide (0.72 mmol, prepared from *n*-butyllithium and diisopropylamine) at -78 °C under an argon atmosphere. The solution was stirred at -78 °C for 15 min, then at -50 °C for 10 min to complete the lithiation. Isoamyl nitrite (90 μl, 0.70 mmol) was added to the resulting lithium enolate at -78 °C, and the reaction mixture was stirred at that temperature for 1 h. The reaction was quenched with acetic acid, and the solution was poured into saturated NaCl. The product was extracted with ethyl acetate, and the organic solution was washed with saturated NaCl and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatgraphed on silica gel (eluted with Et_2O: hexane = 1 : 1) to give the less polar oxime **8a** (40.3 mg, 48%) and the polar oxime **8b** (12.1 mg, 15%). Total yield 63%. The stereochemistry of **8a** and **8b** was not determined. **8a**: *Rf* 0.38 (Et_2O: hexane = 1 : 1). $[\alpha]_D^{20}$ $+32.9°$ (c = 1.94, $CHCl_3$). MS *m/e*: 341 ($M^+ - OH$). IR ($CHCl_3$): 3380, 1750 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.30 (6H, s), 1.88 (9H, s), 1.99 (9H, s), 3.92 (1H, dd, J = 11.3, 3.0 Hz), 4.04 (1H, dd, J = 11.3, 3.5 Hz), 4.42 (1H, dd, J = 3.5, 3.0 Hz), 9.64 (1H, br s). **8b**: *Rf* 0.26 (Et_2O: hexane = 1 : 1). $[\alpha]_D^{20}$ $-6.3°$ (c = 0.74, $CHCl_3$). MS *m/e*: 341 ($M^+ - OH$). IR ($CHCl_3$): 3390, 1750 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.32 (6H, s), 1.88 (9H, s), 1.98 (9H, s), 3.86 (2H, d, J = 3.5 Hz), 4.22 (1H, t, J = 3.5 Hz), 8.80 (1H, br s).

(3*S*,4*S*)-1-(*tert*-Butyldimethylsilyl)-3-amino-4-(*tert*-butyldimethylsilyloxymethyl)azetidin-2-one (9)——The mixture of *syn–anti* oxime **8** (94 mg, 0.26 mmol) was dissolved in ethyl acetate (1.0 ml). Platinum oxide was added and the mixture was stirred under a hydrogen atmosphere at room temperature for 7 h. The catalyst was filtered off on a celite pad, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (eluted with Et_2O: hexane = 4 : 1) to give the *cis* amine **9** (65.4 mg, 72%) and the *trans* amine **10** (9.0 mg, 10%). **9**: *Rf* 0.56 (Et_2O). $[\alpha]_D^{20}$ $-26.5°$ (c = 0.93, $CHCl_3$). IR ($CHCl_3$): 3420, 1735 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.11 (6H, s), 0.19 (3H, s), 0.29 (3H, s), 0.91 (9H, s), 0.95 (9H, s), 1.96 (2H, s), 3.60—3.76 (1H, m), 3.88 (2H, s), 4.23 (1H, d, J = 5.8 Hz). **10**: *Rf* 0.43 (Et_2O). $[\alpha]_D^{20}$ $+6.5°$ (c = 0.99, $CHCl_3$). IR ($CHCl_3$): 3350, 1740 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.23 (3H, s), 0.25 (3H, s), 0.90 (9H, s), 0.96 (9H, s), 1.95 (2H, s), 3.35 (1H, dt, J = 2.7, 4.5 Hz), 3.64—3.84 (2H, m), 3.94 (1H, d, J = 2.7 Hz).

(3*S*,4*S*)-1-(*tert*-Butyldimethylsilyl)-3-benzyloxycarbonylamino-4-(*tert*-butyldimethylsilyloxymethyl)azetidin-2-one (11)——A mixture of the *cis* amine **9** (91 mg, 0.26 mmol), sodium bicarbonate (31 mg, 0.37 mmol) and benzyl chloroformate (45 μl, 0.32 mmol) in THF (1 ml)–water (0.5 ml) was stirred at 0 °C for 2 h. The reaction mixture was poured into saturated NaCl, and the product was extracted with ethyl acetate. The organic solution was washed with saturated NaCl and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with Et_2O: hexane = 6 : 5) to give **11** (126 mg, quant). $[\alpha]_D^{20}$ $-11.6°$ (c = 1.25, $CHCl_3$). MS *m/e*: 478 (M^+). IR ($CHCl_3$): 3450, 1745, 1720 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.20 (3H, s), 0.31 (3H, s), 0.90 (9H, s), 0.96 (9H, s), 3.68—3.95 (3H, m), 5.12 (2H, s), 5.22 (1H, dd, J = 10.5, 5.5 Hz), 5.77 (1H, br d, J = 10.5 Hz), 7.32 (5H, s).

(3*S*,4*S*)-3-Benzyloxycarbonylamino-4-hydroxymethylazetidin-2-one (12)——A 2 N HCl solution (1.0 ml) was added to a methanol solution (3.0 ml) of the protected β-lactam **11** (413 mg, 0.86 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The solution was neutralized with saturated $NaHCO_3$, and most of the methanol was removed under reduced pressure. The remaining solution was poured into saturated NaCl, and the product was extracted with ethyl acetate. The organic solution was washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the alcohol **12** (180 mg, 83%). mp 129.5—130.0 °C (recrystallized from AcOEt–*n*-hexane). *Anal.* Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 11.20; N, 5.64. Found: C, 57.32; H, 10.99; N, 10.99. $[\alpha]_D^{20}$ $+8.9°$ (c = 1.0, $CHCl_3$). MS *m/e*: 250 (M^+), 233 ($M^+ - OH$). IR ($CHCl_3$): 3470, 1765, 1720 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.40—3.88 (3H, m), 4.96—5.18 (1H, m), 5.04 (2H, s), 6.46 (1H, br d, J = 10 Hz), 7.19 (1H, s), 7.28 (5H, s).

(3*S*,4*S*)-3-Benzyloxycarbonylamino-4-methoxycarbonylazetidin-2-one (13)——Jones reagent (8 N solution) was added to an acetone solution (3 ml) of the alcohol **12** (110 mg, 0.44 mmol) until the orange color did not fade, and the reaction mixture was stirred at room temperature for 2.5 h. Isopropyl alcohol was added to the reaction mixture to destroy the excess oxidant at 0 °C. The mixture was poured into saturated NaCl, and the product was extracted with ethyl acetate. The organic solution was washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was treated with ethereal diazomethane. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with Et_2O: *n*-hexane = 8 : 1) to give the methyl ester **13** (86 mg, 70%). mp 120—120.5 °C (recrystallized from chloroform–*n*-hexane). *Anal.* Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.19; H, 5.08; N, 9.80. $[\alpha]_D^{20}$ $+87.7°$ (c = 0.86, $CHCl_3$). IR ($CHCl_3$): 1785, 1740 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.63 (3H, s), 4.43 (1H, d, J = 5.5 Hz), 5.10 (2H, s), 5.39 (1H, dd, J = 10, 5.5 Hz), 6.0 (1H, d, 10 Hz), 6.70 (1H, s), 7.32 (5H, s).

(4*S*)-1-(*p*-Methoxybenzyl)-4-hydroxymethylazetidin-2-one (15)——A mixture of the β-lactam **6** (1.71 g, 7.94 mmol), silver oxide (1.29 g, 5.56 mmol) and *p*-methoxybenzyl chloride (2.32 ml, 15.9 mmol) in acetonitrile (8 ml) was heated under reflux in the dark under an argon atmosphere. After 3 h, silver oxide (0.258 g, 1.11 mmol) and *p*-methoxybenzyl chloride (0.46 ml, 3.2 mmol) were added, and the reaction mixture was heated for another 4 h. The insoluble materials were filtered off and the solvent was removed under reduced pressure. The resulting crude β-lactam **14** was dissolved in methanol (15 ml), and 1 N HCl (3 ml) was added to the solution at 0 °C. The reaction mixture was stirred at room temperature for 1 h, and then neutralized with saturated $NaHCO_3$. The solvent was removed under reduced pressure, and the product was extracted with chloroform. The extract was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure, then the residue was chromatographed on silica gel (eluted with Et_2O then AcOEt) to give the alcohol **15** (1.57 g, 89%, 2 steps). mp 68—69 °C (recrystallized from Et_2O–*n*-hexane). *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.34; H, 6.86; N, 6.19. $[\alpha]_D^{20}$ +8.8° (c=1.0, $CHCl_3$). MS *m/e*: 221 (M^+), 190 (M^+-CH_2OH). IR ($CHCl_3$): 3330, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (1H, s), 2.75 (1H, dd, J=14.5, 2.0 Hz), 2.95 (1H, dd, J=14.5, 4.5 Hz), 3.62 (3H, m), 3.80 (3H, s), 4.36 (2H, s), 6.86 (2H, d, J=9 Hz), 7.22 (2H, d, J=9 Hz).

(4*S*)-1-(*p*-Methoxybenzyl)-4-(1′-hydroxyethyl)azetidin-2-one (17*S*) and (17*R*)——DMSO (450 μl, 6.4 mmol) was added to a methylene chloride solution (5.0 ml) of oxalyl chloride (280 μl, 3.2 mmol) at −70 C° under an argon atmosphere. Then the alcohol **15** (523 mg, 2.36 mmol) in methylene chloride (1.8 ml) was added dropwise, and stirring was continued for an additional 15 min. Next, triethylamine (1.7 ml, 12.2 mmol) was added, and the reaction mixture was stirred for 5 min and allowed to warm to room temperature. The mixture was poured into water and the product was extracted with methylene chloride. The organic solution was washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was applied to a short column of silica gel (eluted with $CHCl_3$: acetone = 5 : 1) for partial purification to give the crude aldehyde **16** (682 mg). This was dissolved in ether (3.5 ml)–THF (4 ml), and the solution was added to methylmagnesium bromide (6.2 mmol) in ether (7 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 2.5 h. The reaction was quenched with 2 N HCl, and the product was extracted with ethyl acetate. The organic solution was washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with Et_2O) to give the less polar isomer **17*S*** (253 mg, 45%) and the polar isomer **17*R*** (176 mg, 32%). **17*S***: mp 77.5—78.5 °C (recrystallized from Et_2O–*n*-hexane). *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.42; H, 7.54; N, 6.18. $[\alpha]_D^{20}$ +38.2° (c=1.19, $CHCl_3$). MS *m/e*: 235 (M^+). IR ($CHCl_3$): 3430, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, d, J=6.2 Hz), 1.70 (1H, s, OH), 2.52 (1H, dd, J=14.5, 2.6 Hz), 2.95 (1H, dd, J=14.5, 5.0 Hz), 3.38 (1H, ddd, J=7.5, 5.0, 2.6 Hz), 3.70 (1H, m), 3.79 (3H, s), 4.34 (1H, d, J=15.2 Hz), 4.50 (1H, d, J=15.2 Hz), 6.85 (2H, d, J=8.8 Hz), 7.23 (2H, d, J=8.8 Hz). **17*R***: mp 57—59 °C (recrystallized from Et_2O–*n*-hexane). *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.07; H, 7.28; N, 6.00. $[\alpha]_D^{20}$ −35.2° (c=0.50, $CHCl_3$). MS *m/e*: 235 (M^+). IR ($CHCl_3$): 3430, 1735 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, d, J=6.6 Hz), 1.69 (1H, s, OH), 2.74 (1H, dd, J=14.5, 5.0 Hz), 2.92 (1H, dd, J=14.5, 3.0 Hz), 3.46 (1H, m), 3.72 (1H, m), 3.81 (3H, s), 4.34 (2H, s), 6.88 (2H, d, J=8.4 Hz), 7.22 (2H, d, J=8.4 Hz).

Methyl (2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)butanoate (19)——A mixture of *N*-Z-L-threonine methyl ester **18** (5.06 g, 20 mmol), triethylamine (4.12 g, 29.6 mmol), *tert*-butyldimethylsilyl chloride (4.34 g, 28.8 mmol) and 4-(dimethylamino)pyridine as a catalyst (200 mg, 1.6 mmol) in DMF (40 ml) was heated at 40 °C for 8.5 h under an argon atmosphere. The reaction mixture was poured into ice water, and the produce was extracted with ether. The organic solution was washed with water and then with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel to give the silyl derivative **19** (7.14 g, 94%). $[\alpha]_D^{20}$ −5.84° (c=1.08, $CHCl_3$). MS *m/e*: 382 (M^++1). IR ($CHCl_3$): 3450, 1750, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.01 (3H, s), 0.05 (3H, s), 0.86 (9H, s), 1.22 (3H, d, J=6.0 Hz), 3.73 (3H, s), 4.28 (1H, dd, J=10.0, 2.0 Hz), 4.45 (1H, dq, J=2.0, 6.0 Hz), 5.15 (2H, s), 5.46 (1H, d, J=10.0 Hz), 7.37 (5H, s).

(2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)butanoic Acid (20)——A 1 N NaOH solution (29 ml, 29 mmol) was added to a methanol solution (60 ml) of the ester **19** (7.0 g, 18.3 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 5 h. Most of the methanol was removed under reduced pressure at below 30 °C, and the aqueous solution was washed with ether to remove the unhydrolyzed ester **19** (0.9 g, 13%). The aqueous solution was made acidic with 2 N HCl, and NaCl was added to give saturation. The product was extracted with ethyl acetate, and the organic solution was washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the carboxylic acid **20** (4.4 g, 65%). mp 158—160 °C (recrystallized from ether). *Anal.* Calcd for $C_{18}H_{29}NO_5Si$: C, 58.82; H, 7.95; N, 3.81. Found: C, 59.03; H, 8.12; N, 3.99. $[\alpha]_D^{20}$ +15.1° (c=1.0, $CHCl_3$). MS *m/e*: 368 (M^++1). IR (KBr): 3400, 1755, 1735, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.08 (3H, s), 0.87 (9H, s), 1.22 (3H, d, J=6.2 Hz), 4.32 (1H, dd, J=9.0, 2.0 Hz), 4.48 (1H, dq, J=2.0, 6.0 Hz), 5.15 (2H, s), 5.50 (1H, d, J=9 Hz), 7.36 (5H, s), 9.19 (1H, s).

(3*S*,4*R*)-1-Diazo-3-benzyloxycarbonylamino-4-(*tert*-butyldimethylsilyloxy)pentan-2-one (21)——Ethyl chloroformate (690 μl, 7.2 mmol) in ether (3 ml) and triethylamine (780 μl, 7.2 mmol) in ether (3 ml) were added to an ether solution (30 ml) of the carboxylic acid **20** (2.14 g, 5.8 mmol) at −15 °C, and the reaction mixture was stirred at that temperature for 30 min and then at 0 °C for 15 min. Ethereal diazomethane was added to the solution at 0 °C until the yellow color did not fade, and the reaction mixture was stirred at 0 °C for 2.5 h. The organic solution was washed successively with water, saturated $NaHCO_3$ and saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was passed through a short column of silica gel (eluted with Et_2O : *n*-hexane = 1 : 5) to give the crude diazo ketone **21** (1.75 g, 77%). This was used for the next reaction without further purification. IR (neat): 2100, 1720, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (3H, s), 0.05 (3H, s), 0.86 (9H, s), 1.15 (3H, d, J=6.8 Hz), 4.10 (1H, dd, J=8.0, 2.2 Hz), 4.42 (1H, dq, J=2.2, 6.8 Hz), 5.13 (2H, s), 5.57 (1H, s), 6.0 (1H, br), 7.36 (5H, s).

Methyl (3*R*,4*R*)-3-Benzyloxycarbonylamino-4-(*tert*-butyldimethylsilyloxy)pentanoate (22)——A triethylamine solution (1.8 ml) of silver benzoate (18 mg) was added to a methanol solution (20 ml) of the diazo ketone **21** (1.75 g, 4.5 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the product was extracted with ether. The organic solution was washed successively with saturated $NaHCO_3$, water and saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with Et_2O : *n*-hexane = 1 : 2) to give the methyl ester **22** (1.14 g, 64%). $[\alpha]_D^{20}$ +10.3° (c=1.23, $CHCl_3$). MS *m/e*: 395 (M^+). IR ($CHCl_3$): 3450, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 1.14 (3H, d, J=6.1 Hz), 2.53 (2H, d, J=7.8 Hz), 3.64 (3H, s), 3.84—4.06 (2H, m), 5.07 (1H, m), 5.10 (2H, s), 7.34 (5H, s).

(3*R*,4*R*)-3-Benzyloxycarbonylamino-4-(*tert*-butyldimethylsilyloxy)penatanoic Acid (23)——A mixture of the methyl ester **22** (1.13 g, 2.86 mmol) and 1 N KOH (5.2 ml, 5.2 mmol) in methanol (20 ml) was stirred at room temperature for 23 h. Water was added and the most of the methanol was removed under reduced pressure below 30 °C. The aqueous solution was washed with ether, and was made acidic with 2 N HCl. NaCl was added until saturation, and the product was extracted with ethyl acetate. The organic solution was washed with water and saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude carboxylic acid **23** (1.13 g, quantitative). This was used for the next reaction without purification. $[\alpha]_L^{20}$ +12.2° (c=1.08, $CHCl_3$). IR ($CHCl_3$): 3450, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (6H, s), 0.88 (9H, s), 1.14 (3H, d, J=6.2 Hz), 2.57 (2H, d, J=6.5 Hz), 4.0 (2H, m), 5.10 (2H, s), 5.12 (1H, br), 7.14 (5H, s).

(3*R*,4*R*)-3-Amino-4-(*tert*-butyldimethylsilyloxy)pentanoic Acid (24)——The crude carboxylic acid **23** (1.13 g, obtained in the above reaction) was dissolved in methanol (10 ml), and 10% Pd–C was added. The mixture was stirred under a hydrogen atmosphere for 1 h. The catalyst was filtered off on a celite pad, and removal of the solvent under reduced pressure gave the β-amino acid **24** (652 mg, 92% from **21**). mp 171—174 °C (recrystallized from methanol–diisopropyl ether). *Anal.* Calcd for $C_{11}H_{25}NO_3Si$: C, 53.40; H, 10.19; N, 5.66. Found: C, 53.42; H, 10.37; N, 5.56. $[\alpha]_D^{20}$ +11.1° (c=1.00, MeOH). MS *m/e*: 248 (M^++1). IR (KBr): 1545 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.14 (6H, s), 0.93 (9H, s), 1.25 (3H, d, J=6.3 Hz), 2.36 (1H, d, J=2.5 Hz), 2.44 (1H, s), 3.28 (1H, m), 3.96 (1H, dq, J=4.5, 6.3 Hz).

(3*R*,4*R*)-3-(*p*-Methoxybenzylamino)-4-(*tert*-butyldimethylsilyloxy)penatanoic Acid (25)——A mixture of the β-amino acid **24** (247 mg, 1.0 mmol) and *p*-methoxybenzaldehyde (0.22 ml, 1.8 mmol) in ethanol (5 ml) was stirred at room temperature for 45 min. Then 10% Pd–C was added, and the mixture was stirred under a hydrogen atmosphere for 20 h at room temperature, and at 40 °C for 4 h. The catalyst was filtered off on a celite pad, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (eluted with $CHCl_3$: MeOH = 10 : 1) to give the *p*-methoxybenzyl derivative **25** (266 mg, 72%). $[\alpha]_D^{20}$ −20.1° (c=1.05, $CHCl_3$). MS *m/e*: 367 (M^+). IR ($CHCl_3$): 1715, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (3H, s), 0.07 (3H, s), 0.84 (9H, s), 1.22 (3H, d, J=6.2 Hz), 2.31 (1H, dd, J=17.0, 5.2 Hz), 2.60 (1H, dd, J=17.0, 4.7 Hz), 2.88 (1H, m), 3.72—4.05 (3H, m), 3.80 (3H, s), 6.87 (2H, d, J=8.8 Hz), 7.26 (2H, d, J=8.8 Hz), 7.90 (2H, br).

(4*R*)-1-(*p*-Methoxybenzyl)-4-[(1′*R*)-1′-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one (26)——The *N*-*p*-methoxybenzyl derivative **25** (144 mg, 0.392 mmol) and 2,2′-dipyridyl disulfide (104 mg, 0.47 mmol) were dissolved in acetonitrile (30 ml), and the solution was heated at 80 °C. To this heated solution, triphenylphosphine (124 mg, 0.47 mmol) in acetonitrile (10 ml) was slowly added over a period of 1 h. The whole was heated at 80 °C for another 2 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel to give the β-lactam **26** (105 mg, 77%). $[\alpha]_D^{20}$ −42.8° (c=0.50, $CHCl_3$). MS *m/e*: 349 (M^+). IR ($CHCl_3$): 1735, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.92 (9H, s), 1.08 (3H, d, J=6.2 Hz), 2.56 (1H, dd, J=14.7, 2.5 Hz), 2.86 (1H, dd, J=14.7, 5.1 Hz), 4.38 (1H, ddd, J=6.1, 5.1, 2.5 Hz), 4.80 (3H, s), 4.84 (1H, m), 5.06 (1H, d, J=14.8 Hz), 5.70 (1H, d, J=14.8 Hz), 7.84 (1H, d, J=8.8 Hz), 8.20 (2H, d, J=8.8 Hz).

(4*R*)-1-(*p*-Methoxybenzyl)-4-[(1′*R*)-1′-hydroxyethyl]azetidin-2-one (27)——A 2 N HCl solution (0.4 ml, 0.8 mmol) was added to a methanol solution (3 ml) of the β-lactam **26** (60.9 mg, 0.17 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 9 h and neutralized with saturated $NaHCO_3$. Most of the methanol was removed under reduced pressure. The mixture was poured into saturated NaCl, and the product was extracted with ethyl acetate. The organic solution was washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with Et_2O) to give the authentic β-lactam **27** (35.4 mg, 86%). $[\alpha]_D^{20}$ −35.5° (c=1.77, $CHCl_3$). MS *m/e*: 235 (M^+). IR ($CHCl_3$): 3430, 1735, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, d, J=6.2 Hz), 1.96 (1H, s, OH), 2.54 (1H, dd, J=14.7, 2.6 Hz), 2.92 (1H, dd, J=14.7, 5.0 Hz), 3.38 (1H, ddd, J=7.5, 5.0, 2.6 Hz), 3.70 (1H, m), 3.80 (3H, s), 4.32 (1H, d, J=15.0 Hz), 4.52

(1H, d, J=15.0 Hz), 6.86 (2H, d, J=8.8 Hz), 7.23 (2H, d, J=8.8 Hz).

(4*S*)-1-(*p*-Methoxybenzyl)-4-[(1′*S*)-1′-methoxyethyl]azetidin-2-one (28*S*)——The alcohol **17*S*** (35.8 mg, 0.15 mmol) in THF (0.7 ml) was added to a THF suspension (1.4 ml) of sodium hydride in mineral oil (14.6 mg, 0.3 mmol) at 0 °C under an arogon atmosphere, and the mixture was stirred at room temperature for 10 min. Then methyl iodide (76 μl, 1.22 mmol) was added. The reaction mixture was stirred at room temperature for 6 h, and poured into ice water, and the product was extracted with ethyl acetate. The organic solution was washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (AcOEt : *n*-hexane = 10 : 1) to give the methyl ether **28*S*** (30.4 mg, 80%). $[\alpha]_D^{20}$ +50.4 ° (c=1.00, $CHCl_3$). MS *m/e*: 249 (M^+). IR ($CHCl_3$): 1735, 1610 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, J=5.6 Hz), 2.50 (1H, dd, J=14.5, 2.1 Hz), 2.94 (1H, dd, J=14.5, 5.0 Hz), 3.23 (3H, s), 3.36 (1H, m), 3.75 (1H, m), 3.79 (3H, s), 4.20 (1H, d, J=14.0 Hz), 4.54 (1H, d, J=14.0 Hz), 6.84 (2H, d, J=8.4 Hz), 7.22 (2H, d, J=8.4 Hz).

In a similar manner, **28*R*** was obtained in 80% yield from **17*R***. **28*R***: $[\alpha]_D^{20}$ +26.1 ° (c=0.95, $CHCl_3$). MS *m/e*: 249 (M^+). IR ($CHCl_3$): 1730, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, d, J=6.4 Hz), 2.80 (2H, d, J=3.8 Hz), 3.23 (3H, s), 3.46 (2H, m), 3.80 (3H, s), 4.06 (1H, d, J=15.0 Hz), 4.58 (1H, d, J=15.0 Hz), 6.85 (2H, d, J=8.8 Hz), 7.18 (2H, d, J=8.8 Hz).

(4*S*)-1-(*p*-Methoxybenzyl)-3-hydroxyimino-4-[(1′*S*)-1′-methoxyethyl]azetidin-2-one (29*S*)——The lactam **28*S*** (43.7 mg, 0.18 mmol) in THF (1 ml) was added to a THF solution (2 ml) of lithium hexamethyldisilazide (0.7 mmol, prepared from *n*-butyllithium and hexamethyldisilazane) at −78 °C under an arogon atmosphere, and the mixture was stirred at that temperature for 10 min and then at −50 °C for 10 min. The solution was recooled to −78 °C and isoamyl nitrite (0.19 ml, 1.4 mmol) was added. The reaction mixture was stirred at −50 °C for 1 h, and quanched with saturated NH_4Cl. The solution was poured into saturated NaCl, and the product was extracted with ethyl acetate. The organic solution was washed with saturated NaCl and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with Et_2O) to give the keto oxime **29*S*** (27.3 mg, 49%) as an about 8 : 1 *syn–anti* mixture, with recovery of the starting β-lactam **28*S*** (18.5 mg, 42%). The following spectroscopic data were obtained with the mixture. MS *m/e*: 278 (M^+). IR ($CHCl_3$): 3280, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, J=6.0 Hz), 3.24 (1/9 × 3H, s), 3.30 (8/9 × 3H, s), 3.40—3.96 (1H, m), 3.76 (3H, s), 4.18 (1H, d, J=5.5 Hz), 4.27 (8/9 × 1H, d, J=14.8 Hz), 4.34 (1/9 × 1H, d, J=14.8 Hz), 4.76 (1/9 × 1H, d, J=14.8 Hz), 4.87 (8/9 × 1H, d, J=14.8 Hz), 6.85 (2H, d, J=8.4 Hz), 7.20 (2H, d, J=8.4 Hz), 9.80 (1H, s, =N–OH).

In a similar manner, keto oxime **29*R*** was obtained in 43% yield from **28*R*** along with the recovery of **28*R*** (28.4 mg, 43%). In this case *syn–anti* isomers were separated by preparative thin layer chromatography (developed with Et_2O) to give the less polar isomer **29*R*-a** and the more polar isomer **29*R*-b**. **29*R*-a**: $[\alpha]_D^{20}$ +57.5 ° (c=1.33, $CHCl_3$). MS *m/e*: 278 (M^+). IR ($CHCl_3$): 3300, 1760, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, d, J=6.3 Hz), 3.27 (3H, s), 3.81 (3H, s), 3.85 (1H, dq, J=2.4, 6.3 Hz), 4.16 (1H, d, J=14.8 Hz), 4.42 (1H, d, J=2.4 Hz), 4.88 (1H, d, J=14.8 Hz), 6.86 (2H, d, J=8.8 Hz), 7.21 (2H, d, J=8.8 Hz), 9.24 (1H. br s, =N–OH). **29*R*-b**: $[\alpha]_D^{20}$ +107.7 ° (c=1.37, $CHCl_3$). MS *m/e*: 278 (M^+). IR ($CHCl_3$): 3280, 1750, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, d, J=6.3 Hz), 3.24 (3H, s), 3.55 (1H, dq, J=2.7, 6.3 Hz), 3.81 (3H, s), 4.15 (1H, d, J=2.7 Hz), 4.16 (1H, d, J=14.7 Hz), 4.84 (1H, d, J=14.7 Hz), 6.85 (2H, d, J=8.4 Hz), 7.20 (2H, d, J=8.4 Hz), 8.81 (1H, br s, =N–OH).

(3*S*,4*S*)-1-(*p*-Methoxybenzyl)-3-amino-4-[(1′*S*)-1′-methoxyethyl]azetidin-2-one (30*S*)——The keto oxime **29*S*** (174 mg, 0.63 mmol) in ethyl acetate (3.0 ml) was stirred under a hydrogen atmosphere in the presence of platinum oxide for 12 h. The catalyst was filtered off on a celite pad, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (eluted with $CHCl_3$: MeOH = 9 : 1) to give the *cis* amine **30*S*** (97 mg, 59%) and the *trans* amine **31*S*** (32.1 mg, 19%). **30*S***: *Rf* 0.41 ($CHCl_3$: MeOH = 10 : 1). $[\alpha]_D^{20}$ +48.9 ° (c=0.60, $CHCl_3$). MS *m/e*: 265 (M^+ + 1). IR ($CHCl_3$): 3380, 1740, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, d, J=6.0 Hz), 1.74 (2H, s), 3.29 (3H, s), 3.42 (2H, m), 3.80 (3H, s), 4.10 (1H, d, J=5.0 Hz), 4.12 (1H, d, J=14.5 Hz), 4.68 (1H, d, J=14.5 Hz), 6.82 (2H, d, J=8.8 Hz), 7.17 (2H, d, J=8.8 Hz). **31*S***: *Rf* 0.37 ($CHCl_3$: MeOH = 10 : 1). $[\alpha]_D^{20}$ +96.0 ° (c=0.93, $CHCl_3$). MS *m/e*: 265 (M^+ + 1). IR ($CHCl_3$): 3400, 1740, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=6.4 Hz), 1.70 (2H, s), 3.10 (1H, dd, J=8.4, 2.1 Hz), 3.21 (3H, s), 3.35 (1H, dq, J=6.4, 8.4 Hz), 3.71 (1H, d, J=2.1 Hz), 3.80 (3H, s), 4.18 (1H, d, J=14.7 Hz), 4.50 (1H, d, J=14.7 Hz), 6.84 (2H, d, J=8.4 Hz), 7.20 (2H, d, J=8.4 Hz).

In a similar manner, the treatment of **29*R*-a** with PtO_2–H_2 in ethyl acetate gave the *cis* amine **30*R*** and the *trans* amine **31*R*** in 71% and 9% yields, respectively (*cis*/*trans* = 8). Furthermore, **29*R*-b** afforded **30*R*** and **31*R*** in 69% and 5% yields, respectively (*cis*/*trans* = 14). **30*R***: mp 85.5—86.0 °C (recrystallized from Et_2O–*n*-hexane). *Anal.* Calcd for $C_{14}H_{20}N_2O_3$: C, 63.61; H, 7.63; N, 10.60. Found: C, 63.59; H, 7.86; N, 10.83. *Rf* 0.49 ($CHCl_3$: MeOH = 10 : 1). $[\alpha]_D^{20}$ −43.7 ° (c=1.13, $CHCl_3$). MS *m/e*: 265 (M^+ + 1). IR ($CHCl_3$): 3420, 1740, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=6.6 Hz), 1.77 (2H, s), 3.20 (3H, s), 3.46 (1H, dd, J=5.1, 1.9 Hz), 3.57 (1H, dq, J=1.9, 6.6 Hz), 3.80 (3H, s), 4.06 (1H, d, J=14.8 Hz), 4.21 (1H, d, J=5.1 Hz), 4.55 (1H, d, J=14.8 Hz), 6.85 (2H, d, J=8.8 Hz), 7.18 (2H, d, J=8.8 Hz). **31*R***: *Rf* 0.43 ($CHCl_3$: MeOH = 10 : 1). $[\alpha]_D^{20}$ +81.2 ° (c=0.43, $CHCl_3$). MS *m/e*: 265 (M^+ + 1). IR ($CHCl_3$): 3400, 1740, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, d, J=6.0 Hz), 3.21 (3H, s), 3.04—3.56 (3H, m), 3.80 (3H, s), 4.05 (1H, d, J=15.0 Hz), 4.59 (1H, d, J=15.0 Hz), 6.84 (2H, d, J=8.8 Hz), 7.20 (2H, d, J=8.8 Hz).

(3*S*,4*S*)-1-(*p*-Methoxybenzyl)-3-benzyloxycarbonylamino-4-[(1′*S*)-1′-methoxyethyl]azetidin-2-one (32*S*)——A mixture of the *cis* amine **31*S*** (52.7 mg, 0.2 mmol), $NaHCO_3$ (33.6 mg, 0.4 mmol) and benzyl chloroformate (43 μl, 0.3 mmol) in THF (1.0 ml)–water (0.5 ml) was stirred at 0 °C for 2 h. The mixture was poured into saturated NaCl, and the product was extracted with ethyl acetate. The organic solution was washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with Et_2O) to give the Z-amino derivative **32*S*** (72.5 mg, 91%). mp 100.5—101.5 °C (recrystallized from Et_2O). *Anal.* Calcd for $C_{22}H_{26}N_2O_5$: C, 66.31; H, 6.58; N, 7.03. Found: C, 66.27; H, 6.62; N, 7.12. $[\alpha]_D^{20}$ +64.6° (c=1.00, $CHCl_3$). MS *m/e*: 398 (M^+). IR ($CHCl_3$): 3450, 1750, 1720, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, d, J=6.3 Hz), 3.28 (3H, s), 3.20—3.56 (2H, m), 3.79 (3H, s), 4.10 (1H, d, J=15.2 Hz), 4.72 (1H, d, J=15.2 Hz), 5.04 (1H, dd, J=9.6, 5.0 Hz), 5.10 (2H, s), 5.53 (1H, br d, J=9.6 Hz), 6.82 (2H, d, J=8.4 Hz), 7.19 (2H, d, J=8.4 Hz), 7.32 (5H, s).

In a similar manner, **32*R*** was obtained in 96% yield from **30*R***. **32*R***: mp 121—122 °C (recrystallized from Et_2O). *Anal.* Calcd for $C_{22}H_{26}N_2O_5$: C, 66.31; H, 6.58; N, 7.03. Found; C, 66.05; H, 6.54; N, 6.95. $[\alpha]_D^{20}$ −49.8° (c=1.07, $CHCl_3$). MS *m/e*: 398 (M^+). IR ($CHCl_3$): 3420, 1750, 1720, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, d, J=6.8 Hz), 3.12 (3H, s), 3.48 (1H, dq, J=2.0, 6.8 Hz), 3.52 (1H, dd, J=5.0, 2.0 Hz), 3.80 (3H, s), 4.15 (1H, d, J=16.0 Hz), 4.47 (1H, d, J=16.0 Hz), 5.10 (2H, s), 5.24 (1H, dd, J=10.8, 5.0 Hz), 5.92 (1H, br d, J=10.8 Hz), 6.84 (2H, d, J=8.0 Hz), 7.17 (2H, d, J=8.0 Hz), 7.33 (5H, s).

(3*S*,4*S*)-3-Benzyloxycarbonylamino-4-[(1′*S*)-1′-methoxyethyl]azetidin-2-one (33*S*)——A mixture of the β-lactam **32*S*** (90.7 mg, 0.23 mmol), potassium persulfate (177 mg, 0.65 mmol), dipotassium hydrogen phosphate (142 mg, 0.82 mmol) and cupric sulfate pentahydrate (17.7 mg, 0.07 mmol) in acetonitrile (2.5 ml) and water (1.3 ml) was heated at 95 °C under an argon atmosphere for 2 h. During the reaction, dipotassium hydrogen phosphate was added in a small portion to maintain the medium at pH 6—7. The reaction mixture was poured into saturated NaCl, and the product was extracted with ethyl acetate. The organic solution was washed with saturated NaCl, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with ethyl acetate) to give the β-lactam **33*S*** (42.3 mg, 67%). mp 102—103 °C (recrystallized from Et_2O–n-hexane). *Anal.* Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.25; H, 6.43; N, 10.04. $[\alpha]_D^{20}$ +68.6° (c=0.50, $CHCl_3$). MS *m/e*: 279 (M^++1). IR ($CHCl_3$): 3450, 1770, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, d, J=6.4 Hz), 3.31 (3H, s), 3.39 (1H, dq, J=5.5, 6.4 Hz), 3.65 (1H, dd, J=5.5, 5.1 Hz), 5.10 (1H, dd, J=9.6, 5.1 Hz), 5.13 (2H, s), 6.05 (1H, br d, J=9.6 Hz), 6.68 (1H, br s), 7.33 (5H, s).

In a similar manner, **33*R*** was obtained in 66% yield from **32*R***. **33*R***: mp 175—176 °C (recrystallized from AcOEt–n-hexane). *Anal.* Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N; 10.07. Found: C, 60.43; H, 6.58; N, 10.18. $[\alpha]_D^{20}$ −27.8° (c=1.00, $CHCl_3$). MS *m/e*: 279 (M^++1). IR ($CHCl_3$): 3420, 1770, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=6.4 Hz), 3.36 (3H, s), 3.60 (1H, dq, J=2.7, 6.4 Hz), 3.74 (1H, dd, J=5.3, 2.7 Hz), 5.12 (2H, s), 5.26 (1H, dd, J=10.4, 5.3 Hz), 5.93 (1H, br d, J=10.4 Hz), 6.0 (1H, br s), 7.35 (5H, s).

(3*S*,4*S*)-3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-(1′*S*)-1′-methoxyethyl]azetidin-2-one (34*S*)——The Z-amino β-lactam **33*S*** (111 mg, 0.40 mmol) in methanol (2 ml) was stirred in the presence of 10% Pd–C under a hydrogen atmosphere for 2 h. The catalyst was filtered off on a celite pad, and the solvent was removed under reduced pressure to give the crude amino β-lactam. This was dissolved in DMF (4 ml). (*Z*)-2-(2-Chloroacetamino-4-thiazol-yl)-2-methoxyiminoacetic acid (181 mg, 0.65 mmol), 1-hydroxybenzotriazole hydrate (132 mg, 0.65 mmol) and *N,N′*-dicyclohexylcarbodiimide (134 mg, 0.88 mmol) were added to the above solution at 0 °C. The reaction mixture was stirred at room temperature overnight. The insoluble material was filtered off, and the solvent was removed under reduced pressure. DMF was added to the residue, insoluble material was filtered off, and then DMF was removed under reduced pressure. This was repeated twice, and the residue was washed with ethyl acetate to give the crude β-lactam **34*S*** (102 mg, 63%). This was used for the next step without further purification. mp >230 °C (dec.). IR (KBr): 3310, 1735, 1665 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.03 (3H, d, J=6.0 Hz), 3.22 (3H, s), 3.44 (2H, m), 3.88 (3H, s), 4.37 (2H, s), 5.16 (1H, dd, J=8.8, 5.2 Hz), 7.40 (1H, s), 9.23 (1H, br d, J=8.8 Hz).

In a similar manner, **34*R*** was obtained in 84% yield from **33*R***. **34*R***: mp >210 °C (dec.). IR (KBr): 3280, 1758, 1655 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.08 (3H, d, J=6.0 Hz), 3.15 (3H, s), 3.44—3.67 (2H, m), 3.89 (3H, s), 4.38 (2H, s), 5.28 (1H, dd, J=9.0, 5.0 Hz), 7.36 (1H, s), 9.18 (1H, br d, J=9.0 Hz).

Sodium (3*S*, 4*S*)-3-[2-(2-Chloroacetamidothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-[(1′*S*)-1′-methoxyethyl]-2-oxo-azetidin-1-sulfonate (35*S*)——A mixture of the β-lactam **34*S*** (88.7 mg, 0.22 mmol) and sulfur trioxide–pyridine complex (104 mg, 0.65 mmol) in DMF (2 ml) and methylene chloride (2 ml) was stirred under an argon atmosphere at 40 °C for 2 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with $CHCl_3$: MeOH : H_2O = 70 : 30 : 5). The product was subjected to chromatography on Dowex 50 W × 2 H^+ form (1 ml) to give the sulfonated β-lactam **35*S*** (50.5 mg, 46%) as a white powder after lyophilization. mp >210 °C (dec.). IR (KBr): 3440, 1765, 1665 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.32 (3H, d, J=6.5 Hz), 3.39 (3H, s), 3.62 (1H, dd, J=6.5, 4.0 Hz), 4.04 (3H, s), 4.36 (1H, m), 4.43 (2H, s), 5.52 (1H, d, J=6.0 Hz), 7.50 (1H, s).

In a similar manner, **35*R*** was obtained in 60% yield from **34*R***. **35*R***: mp >210 °C (dec.). $[\alpha]_D^{20}$ −33.6° (c=0.57, H_2O). IR (KBr): 3460, 1778, 1678 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.26 (3H, d, J=6.5 Hz), 3.36 (3H, s), 3.98 (1H, m), 4.02 (3H, s), 4.34 (1H, dd, J=5.8, 2.7 Hz), 4.42 (2H, s), 5.64 (1H, d, J=5.8 Hz), 7.50 (1H, s).

Sodium (3*S*,4*S*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-[(1′*S*)-1′-methoxyethyl]-2-oxoazetidin-1-sulfonate (36*S*)——A mixture of the chloroacetamido derivative **35***S* (39.4 mg, 0.086 mmol) and sodium *N*-methyl dithiocarbamate (20.9 mg, 0.16 mmol) was stirred at room temperature for 3 h. Water was added, and the aqueous solution was washed with ether, then concentrated to the volume of about 1 ml. This concentrate was chromatographed on CHP-20 (20 ml, eluted with water) followed by lyophilization to give the monobactam analog **36***S* as a white powder (28.6 mg, 86%). mp >227 °C (dec.). $[\alpha]_D^{20}$ +24.4° (c=0.81, H_2O). IR (KBr): 3420, 1765, 1660 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.32 (3H, d, J=6.5 Hz), 3.29 (3H, s), 3.59 (1H, dq, J=4.0, 6.5 Hz), 3.99 (3H, s), 4.32 (1H, dd, J=5.8, 4.0 Hz), 5.50 (1H, d, J=5.8 Hz), 6.98 (1H, s).

In a similar manner, the isomeric **36***R* was obtained in 64% yield from **35***R*. **36***R*: mp 224 °C (dec.). $[\alpha]_D^{20}$ −28.5° (c=0.75, H_2O). IR (KBr): 3420, 1760, 1650 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.25 (3H, d, J=6.8 Hz), 3.36 (3H, s), 3.98 (3H, s), 4.0 (1H, m), 4.33 (1H, dd, J=5.8, 2.7 Hz), 5.62 (1H, d, J=5.8 Hz), 6.98 (1H, s).

References and Notes

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