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Synthesis of *cis*-Substituted β-Lactams, Potential Intermediates for *cis*-Carbapenems, from L-Aspartic Acid[1)]

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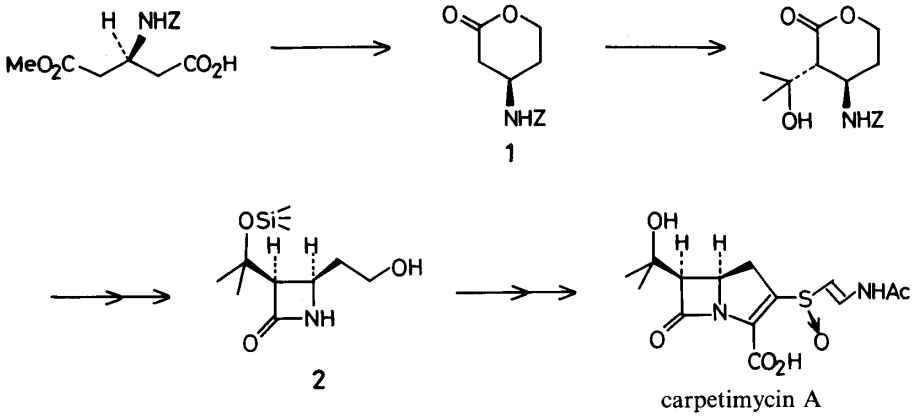
(3*S*)-3-Benzyloxycarbonylamino-γ-butyrolactone was prepared by the regioselective reduction of L-aspartic acid. Alkylation and aldol condensation of the γ-butyrolactone afforded the *trans* isomer selectively. The resulting 2,3-*trans* γ-butyrolactone was hydrolyzed and then cyclized to give the 3,4-*cis* β-lactam. By taking advantage of this strategy, key intermediates of epi-PS-5 and carpetimycins were synthesized.

Keywords——*cis*-carbapenem; L-aspartic acid; carpetimycin A; epi-PS-5

The recent interest in β-lactam antibiotics has been mainly focused on carbapenems,[2a)] penems[2b)] and monobactams.[2c] In these β-lactam antibiotics, the *R*-configuration at C_5 in carbapenems and penems and *S*-configuration at C_3 in the monobactams are considered to be essential for the biological activities. Recently, we have shown that a chemicoenzymatic approach is an excellent methodology for the enantio- and stereoselective synthesis of all types of carbapenem antibiotics[3)] (*trans*-, *cis*- and ene-type). This strategy is based on the creation of novel chiral synthons by enzyme-mediated asymmetric hydrolysis of prochiral diesters.[4)] Another interesting and enantioselective approach to carbapenem antibiotics is to employ L-aspartic acid as a readily available synthon.[5)] For instance, L-aspartic acid was first converted into azetidin-2-one, from which thienamycin was successfully synthesized by the Merck group.[5a] However, this approach is not suitable for *cis*-carbapenems such as carpetimycins because the introduction of side chains at C_3 in a *cis* orientation with respect to the β-lactam ring is not easy. The alkylation of 4-substituted azetidin-2-ones generally affords the thermodynamically more stable *trans* isomers.[3a,6)] In our total synthesis of carpetimycin A by the chemicoenzymatic approach, this stereochemical problem was solved by introducing a hydroxyisopropyl group into the δ-lactone **1** in a *trans* manner, followed by recyclization to



1 2 carpetimycin A

Chart 1

the 3,4-*cis*-β-lactam **2**.[3b] Thus, a thermodynamically less stable isomer with a *cis* relationship in the β-lactam ring was derived from the thermodynamically more stable *trans* substituted δ-lactone (Chart 1). In a similar manner, the chiral γ-lactone **5** could also be considered as a useful intermediate for the synthesis of *cis*-carbapenems, as shown in Chart 2. The chiral γ-

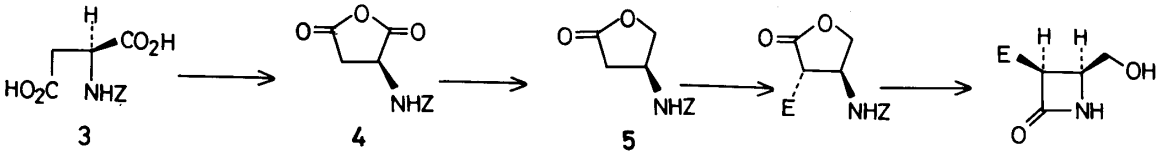
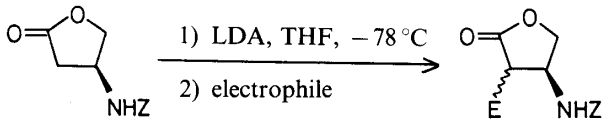


Chart 2

lactone **5** can be derived from L-aspartic acid by the regioselective reduction of the anhydride **4**.[7] In this paper, we wish to report a new synthetic approach to *cis*-carbapenem antibiotics starting with L-aspartic acid.

Anhydride formation from L-aspartic acid was most easily carried out by the procedure of Bergmann and Zervas[8] (Ac_2O, heat), but we observed that complete racemization took place under the reaction conditions. Therefore, we tried other dehydration procedures, and found that the racemization could be completely suppressed by the thionyl chloride method to afford the anhydride **4**, ($[\alpha]_D^{20}$ −41.9 °(c=1.08, AcOH); lit.[8] $[\alpha]_D^{19}$ −39.8 ° (AcOH)), in 93% yield. The regioselective reduction of the anhydride was efficiently accomplished with sodium borohydride, and the resulting hydroxy acid was directly treated with conc HCl–EtOH in one pot to give the γ-lactone **5** in 72% yield. The dianion of the γ-lactone **5** was generated with lithium diisopropylamide in tetrahydrofuran (THF) at −78 °C, and was treated with various electrophiles. The results are summarized in Table I. The stereoselectivity in the alkylation is

Table I.



5 **6—9**

Electrophile	Product	Conditions	Yield (%)	*trans* : *cis*
MeI	**6** (E=Me)	−78—40 °C	70	4 : 1
EtI	**7** (E=Et)	−78— 0 °C[a]	55	4 : 1
iso-PrI	**8** (E=iso-Pr)	−78—10 °C[a]	15	>95 : <5
Acetone	**9** (E=Me_2CH–CH(OH)–)	−78 °C	84	>95 : <5

a) Alkylation was carried out in the presence of HMPT.

not very high, favoring the *trans* isomers in about 4 to 1 ratio. With bulky isopropyl iodide, the *trans* isomer **8** was preferentially obtained, but in low yield. In this case, the starting γ-butyrolactone **5** was recovered in 39% yield. On the other hand, aldol reaction with acetone proceeded smoothly, and the aldol **9** was obtained in 84% yield. In this reaction, the formation of the corresponding *cis* isomer was hardly detected. The high yield and stereoselectivity could be explained by considering the equilibrium in favor of the aldol product that affords exclusively the thermodynamically more stable *trans* isomer **9**.[9] The γ-lactones **7** and **9** were then converted into the β-lactams **12** and **15**, which are considered as key intermediates for epi-PS-5 and carpetimycin A. Thus, the diastereomeric mixture of the

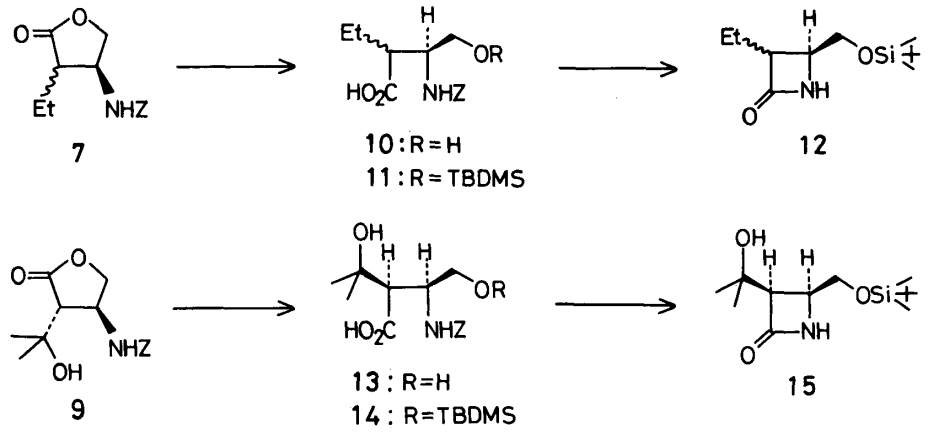


Chart 3

lactone **7** was hydrolyzed with 1 N NaOH in methanol to afford the hydroxy acid **10**. The selective protection of the hydroxyl group was carried out by silylation of both the hydroxyl and the carboxyl group, followed by partial deprotection with 1 N HCl to give the carboxylic acid **11**. After hydrogenolysis of the benzyloxycarbonyl group, the resulting β-amino acid was cyclized by the Ph_3P–PySSPy–CH_3CN method[10] to afford a mixture of *cis* and *trans* β-lactam **12** (*cis*: *trans* = 4 : 1) in 51% yield. The stereochemistry and the ratio were determined from the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. The C_3 proton of the major isomer appeared at δ 3.12 with $J_{3,4} = 5$ Hz, and that of the minor isomer at δ 2.70 with $J_{3,4} < 2$ Hz.

In a similar manner, the aldol product **9** was converted into the *cis* β-lactam **15**. The coupling constant ($J_{3,4} = 5.0$ Hz) clearly supported the *cis* stereochemistry of **15**.

Experimental

Melting points were measured on a Yamato MP-21 apparatus and are uncorrected. Nuclear magnetic resonance 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. Infrared (IR) spectra were recorded 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.

***N*-Z-L-Aspartic Acid Anhydride (4)**——Thionyl chloride (16 ml, 220 mmol) was added to a suspension of Z-L-aspartic acid (5.89 g, 22.1 mmol) in ethyl acetate (35 ml), and the reaction mixture was stirred at room temperature for 1 h. The solvent and excess thionyl chloride were removed under reduced pressure. Trituration of the residue with anhydrous Et_2O–petroleum ether gave the anhydride **4** (5.10 g, 93%) as fine needles. mp 108—111 °C (lit.[7] 84 °C), $[\alpha]_D^{20}$ −41.9° (c = 1.08, AcOH) (lit.[7] $[\alpha]_D^{19}$ −39.8° (AcOH)). MS *m/e*: 249 (M^+). IR (Nujol): 3380, 1860, 1770, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 2.9 (1H, dd, J = 18, 7.5 Hz), 3.3 (1H, dd, J = 18, 9.5 Hz), 4.5—5.2 (1H, m), 5.2 (2H, s), 7.35 (5H, s), 8.0 (1H, br d, J = 6 Hz).

(3*S*)-3-Benzyloxycarbonylamino-γ-butyrolactone (5)——The anhydride **4** (4.94 g, 20 mmol) in THF (16 ml) was slowly added to a suspension of sodium borohydride (757 mg, 20 mmol) in THF (4 ml) at 0 °C over a period of 15 min. The reaction mixture was stirred at room temperature for 1 h, then conc HCl (4 ml) and EtOH (4 ml) were added, and the whole was heated under reflux for 1.5 h. The reaction mixture was poured into saturated NaCl, and the product was extracted with ethyl acetate (4 times). The extract was successively washed 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 triturated with Et_2O–hexane to give **5** as white crystals (3.38 g, 72%). mp 99—105 °C, $[\alpha]_D^{20}$ −50.1° (c = 1.0, $CHCl_3$). IR (Nujol); 3290, 1775, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.4 (1H, dd, J = 18, 3.5 Hz), 2.85 (1H, dd, J = 18, 7 Hz), 4.05—4.7 (1H, m), 5.1 (2H, s), 5.5—5.9 (1H, br d), 7.3 (5H, s).

(3*S*)-3-Benzyloxycarbonylamino-2-methyl-γ-butyrolactone (6)——The lactone **5** (112 mg, 0.48 mmol) in THF (2.0 ml) was added to a THF solution (2 ml) of lithium diisopropylamide (LDA, 1.04 mmol), prepared from *n*-butyl lithium and diisopropylamine, under an argon atmosphere at −78 °C. After 30 min, methyl iodide (36 μl, 0.58 mmol)

was added at −78 °C, and the reaction mixture was gradually warmed to −40 °C over a period of 1 h. The reaction was quenched with saturated NH_4Cl, and the mixture was poured into saturated NaCl. The product was extracted with methylene chloride. The extract was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (eluted with CH_2Cl_2 : Et_2O = 8 : 1) to give a diastereomeric mixture of **6** (78.6 mg, 70%). The *tran–cis* ratio was determined by ^{1}H-NMR integration. The following spectroscopic data were obtained with the *trans–cis* mixture. IR ($CHCl_3$): 1775, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$)δ: 1.18 (2.4H, d, J = 7 Hz), 1.30 (0.6H, d, J = 7 Hz), 2.50 (0.8H, m), 2.76 (0.2H, m), 3.8—4.6 (3H, m), 5.08 (2H, s), 5.40 (1H, br), 7.32 (5H, s).

(3*S*)-3-Benzyloxycarbonylamino-2-ethyl-γ-butyrolactone (7)——The dianion of **5** was prepared from **5** (85.4 mg, 0.36 mmol) and LDA (0.89 mmol) in THF (4 ml) at −78 °C. Hexamethylphosphoramide (HMPT 1 ml) and ethyl iodide (250 μl, 3.1 mmol) were added to the solution, and the reaction mixture was gradually warmed to 0 °C over 1 h. The reaction was quenched with saturated NH_4Cl. The same work-up as above followed by chromatography on silica gel gave the monoethyl derivative **7** (52.6 mg, 55%) as a *trans–cis* mixture and the diethyl derivative (14.8 mg, 14%). The ratio and the stereochemistry of **7** were determined by correlation with the β-lactam **12**. The following spectroscopic data were obtained with the *trans–cis* mixture. IR ($CHCl_3$): 1775, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$)δ: 1.03 (3H, t, J = 8 Hz), 1.4—1.9 (2H, m), 2.20—2.60 (1H, m), 3.80—4.04 (1H, m), 4.10—4.70 (2H, m), 5.09 (2H, s), 5.45 (1H, br), 7.30 (5H, s).

(2*S*,3*S*)-3-Benzyloxycarbonylamino-2-isopropyl-γ-butyrolactone (8)——The dianion of **5** was prepared from **5** (103.4 mg, 0.44 mmol) and LDA (1.10 mmol) in THF (4 ml) at −78 °C. HMPT (2 ml) and isopropyl iodide (750 μl, 7.5 mmol) were added to the solution, and the reaction mixture was gradually warmed to 10 °C over a period of 1 h. The reaction was quenched with saturated NH_4Cl. The same work-up as above followed by chromatography on silica gel gave **8** (17.7 mg, 15%). Unreacted **5** (40.7 mg, 39%) was also recovered. $[\alpha]_D^{20}$ −34.0° (c = 2.10, $CHCl_3$). IR ($CHCl_3$): 1775, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$)δ: 1.00 (3H, d, J = 7 Hz), 1.02 (3H, d, J = 7 Hz), 1.7—2.4 (2H, m), 3.8—4.05 (1H, m), 4.1—4.6 (2H, m), 5.07 (2H, s), 5.40 (1H, br), 7.30 (5H, s).

(2*R*,3*S*)-3-Benzyloxycarbonylamino-2-[(1-hydroxy-1-methyl)-ethyl]-γ-butyrolactone (9)——The dianion of **5** was prepared from **5** (558.7 mg, 2.38 mmol) and LDA (6.40 mmol) in THF (30 ml) at −78 °C under an argon atmosphere. Acetone (300 μl, 10.83 mmol) was added and the reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched with saturated NH_4Cl, and the mixture was poured into saturated NaCl. The product was extracted with ethyl acetate. After removal of the solvent, the residue was chromatographed on silica gel (eluted with CH_2Cl_2 : Et_2O = 8 : 1) to give **9** as an oil (587.7 mg, 84%). $[\alpha]_D^{20}$ −16.23° (c = 1.98, $CHCl_3$). MS *m/e*: 275 ($M^+ - H_2O$). IR ($CHCl_3$): 3600, 3150, 1765, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, s), 1.36 (3H, s), 2.57 (1H, d, J = 7 Hz), 3.0—3.6 (1H, br s), 3.70—4.06 (1H, m), 4.10—4.64 (2H, m), 5.06 (2H, s), 5.76 (1H, br d, J = 6 Hz), 7.28 (5H, s).

(3*S*)-2-Ethyl-3-benzyloxycarbonylamino-4-(*tert*-butyldimethyl-silyloxy)butanoic Acid (11)——A 1 N NaOH solution (590 μl, 0.59 mmol) was added to a methanol solution (1.0 ml) of the γ-lactone **7** (154.9 mg, 0.59 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 25 min and then at room temperature for 15 min. Water was added, and the unreacted γ-lactone **7** was extracted with methylene chloride (recovered **7**, 9.1 mg, 6%). The aqueous solution was made acidic with 1 N HCl, and the product was extracted with ethyl acetate. The removal of the solvent gave the crude acid **10** as a white powder (142.4 mg, 86%), and this material was used for the next reaction without purification. A mixture of the crude acid **10** (142.4 mg, 0.51 mmol), triethylamine (385 μl, 2.76 mmol) and *tert*-butyldimethylchlorosilane (417.1 mg, 2.77 mmol) in dimethylformamide (DMF 3.0 ml) was stirred at room temperature for 2 h. Ether was added to the reaction mixture, and the ether solution was washed with water several times, then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue (332.8 mg, yellow oil) was dissolved in methanol (5.0 ml). To this solution, 1 N HCl (500 μl) was added at 0 °C, and the reaction mixture was stirred at 0 °C for 15 min. The solution was neutralized with 1 N NaOH (500 μl), and poured into saturated NaCl. The product was extracted with ethyl acetate several times. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with CH_2Cl_2 : Et_2O = 8 : 1, then with Et_2O) to give the acid **11** as a diastereomeric mixture (176.5 mg, 76% from **7**). IR ($CHCl_3$): 1720, 1703 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.02 (6H, s), 0.86 (9H, s), 0.8—1.1 (3H, m), 1.5—1.8 (2H, br), 2.3—2.7 (1H, br), 3.66 (2H, m), 3.96 (1H, m), 5.10 (2H, s), 5.26 (1H, br), 7.32 (5H, s).

(4*S*)-3-Ethyl-4-*tert*-butyldimethylsilyloxymethyl-azetidin-2-one (12)——A methanol solution (2.0 ml) of the Z-amino acid **11** (83.3 mg, 0.21 mmol) was stirred under an H_2 atmosphere in the presence of 10% Pd–C. The catalyst was filtered off on a celite pad, and the removal of the solvent gave the crude β-amino acid (50.1 mg, 91%). This material was used for the next reaction without purification. A mixture of the crude acid (50.1 mg, 0.19 mmol), triphenylphosphine (71.0 mg, 0.27 mmol) and 2,2′-dipyridyl disulfide (55.0 mg, 0.25 mmol) in acetonitrile (30 ml) was heated at 80 °C for 4 h. The solvent was removed under reduced pressure, and the residue was treated with triethylamine (100 μl, 0.72 mmol) and methyl iodide (300 μl, 4.82 mmol) in methylene chloride (2 ml) at 0 °C for 20 min. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with CH_2Cl_2: Et_2O = 8 : 1) to give the β-lactam **12** as a diastereomeric mixture (*cis*: *trans* = 4 : 1) (24.0 mg, 51%). The following spectroscopic data were obtained with the mixture. MS *m/e*: 244 ($M^+ + 1$). IR ($CHCl_3$): 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.90 (9H, s), 1.01 (0.6H, t, J = 7.2 Hz), 1.06 (2.4H, t, J = 7.2 Hz), 1.5—1.9 (2H, m), 2.70

(0.2H, m, $J_{3,4}<2$ Hz), 3.12 (0.8H, m, $J_{3,4}=5$ Hz), 3.2—3.8 (3H, m), 7.06 (1H, br).

(2*R*,3*S*)-2-[(1-Hydroxy-1-methyl)ethyl]-3-benzyloxycarbonyl-amino-4-*tert*-butyldimethylsilyloxybutanoic Acid (14)——A 1 N NaOH solution (460 μl, 0.46 mmol) was added to a methanol solution (2 ml) of the γ-lactone **9** (134.6 mg, 0.46 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 30 min. Water was added, and the unreacted γ-butyrolactone was extracted with methylene chloride. The aqueous solution was made acidic with 1 N HCl, and the product was extracted with ethyl acetate. The solvent was removed under reduced pressure to give the crude acid **13** (132.8 mg, 94%). This was used for the next reaction without purification. A mixture of the crude acid **13** (132.8 mg, 0.43 mmol), triethylamine (180 μl, 1.29 mmol) and *tert*-butyldimethylchlorosilane (199.8 mg, 1.33 mmol) in DMF (4 ml) was stirred at room temperature for 30 min. Ether was added and the solution was washed with water, then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was treated with 1 N HCl (400 μl, 0.4 mmol) in methanol (5 ml) at 0 °C for 10 min. The solution was neutralized with 1 N NaOH and the product was extracted with ethyl acetate. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel (eluted with CH_2Cl_2: Et_2O = 1 : 1) to give the acid **14** as a colorless oil (180.7 mg, 93% from **9**). MS *m/e*: 425 (M^+), 369 (M^+-*tert*-Bu). IR ($CHCl_3$): 3400, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.90 (9H, s), 1.38 (6H, s), 2.74 (1H, d, J=4.6 Hz), 3.62 (1H, dd, J=7.3, 9.5 Hz), 3.82 (1H, dd, J=4.0, 9.5 Hz), 4.2 (1H, m), 5.10 (2H, s), 5.76 (1H, br d, J=8 Hz), 6.4 (1H, br), 7.33 (5H, s).

(3*R*,4*S*)-2-[(1-Hydroxy-1-methyl)ethyl]-3-*tert*-butyldimethylsilyloxymethylazetidin-2-one (15)——A methanol solution (3.0 ml) of the Z-amino acid **14** (104.0 mg, 0.24 mmol) was stirred under an H_2 atmosphere in the presence of 10% Pd–C for 45 min. The catalyst was filtered off on a celite pad, and the removal of the solvent under reduced pressure gave the crude β-amino acid. A mixture of the crude β-amino acid, triphenylphosphine (84.0 mg, 0.32 mmol) and 2, 2′-dipyridyl disulfide (68.0 mg, 0.31 mmol) in acetonitrile (45 ml) was heated at 80 °C for 4 h. The solvent was removed under reduced pressure, and the residue was treated with triethylamine (100 μl, 0.72 mmol) and methyl iodide (400 μl, 6.43 mmol) in methylene chloride (3 ml) at room temperature for 20 min. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (eluted with $CHCl_3$: MeOH = 20 : 1) to give the *cis* β-lactam **15** as a white solid (11.4 mg, 17% from **14**). $[\alpha]_D^{20}$ +15.1 ° (c=1.04, $CHCl_3$): MS *m/e*: 330 (M^+-*tert*-Bu). IR ($CHCl_3$): 3420, 1755 cm^{-1}. ^{1}H-NMR ($CDCl_3$ δ: 0.12 (6H, s), 0.90 (9H, s), 1.32 (3H, s), 1.46 (3H, s), 3.36 (1H, dd, J=1.0, 5.0 Hz), 3.8—4.2 (3H, m), 6.06 (1H, br).

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