A STUDY ON THE SYNTHESIS OF CARUMONAM STARTING FROM AN α-AMINO ACID[1)]

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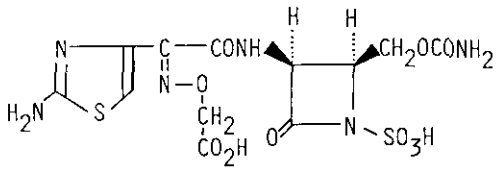
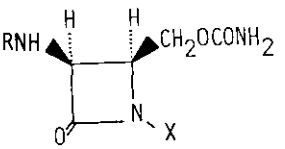
Abstract —— As part of a study on the synthesis of carumonam (1), a method starting from an α-amino acid was investigated. Cycloaddition of the mixed anhydride, derived from carbobenzoxyglycine (7) and isopropyl chloroformate, with the chiral imine (11b), derived from *p*-chlorobenzoyloxyacetaldehyde and L-valine methyl ester, afforded a diastereomeric mixture of two *cis*-β-lactams (13 and 14). The desired (3*S*,4*S*)-isomer (13) was isolated preferentially from the mixture by fractional crystallization. Conversion of 13 into (3*S*,4*S*)-3-benzyloxycarbonylamino-4-carbamoyloxymethyl-2-azetidinone (3), an intermediate in preparing carumonam (1), was achieved by applying anodic oxidation to remove the N_1-substituent of 13.

The extensive studies[2)] of structure activity relationships of sulfazecin[3)] - type compounds led to the selection of carumonam (1, AMA-1080/Ro17-2301), (3*S*,4*S*)-3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-carboxymethoxyiminoacetamido]-4-carbamoyloxymethyl-2-azetidinone-1-sulfonic acid, as a clinical candidate for a new antimicrobial agent, and practical syntheses, especially preparing a key intermediate, (3*S*,4*S*)-3-amino-4-carbamoyloxymethyl-2-azetidinone-1-sulfonic acid (2, CAS), have been intensively studied. In the preceding paper[2h)] we reported an efficient synthetic pathway to 2 starting from (2*R*,3*R*)-epoxysuccinic acid easily accessible by fermentation. Recently a convenient route to 2 *via* (3*S*,4*S*)-3-benzyloxycarbonylamino-4-carbamoyloxymethyl-2-azetidinone (3) was also reported.[2f,4)] This paper describes an alternative synthesis of 3 starting from an α-amino acid.



Carumonam (1)



2 (CAS) R=H, X=SO_3H

3 R=Cbz, X=H

Cbz = $PhCH_2OCO-$

Our planned route to **3** involves two key steps: a) asymmetric cycloaddition of carbobenzoxyglycine (**7**, Cbz-Gly) with the chiral imine (**6**), derived from the ester of an α-amino acid (**4**) and the *O*-substituted hydroxyacetaldehyde (**5**), and b) anodic oxidation to remove the N_1-substituent of the resulting β-lactam (**8**) (Chart 1).

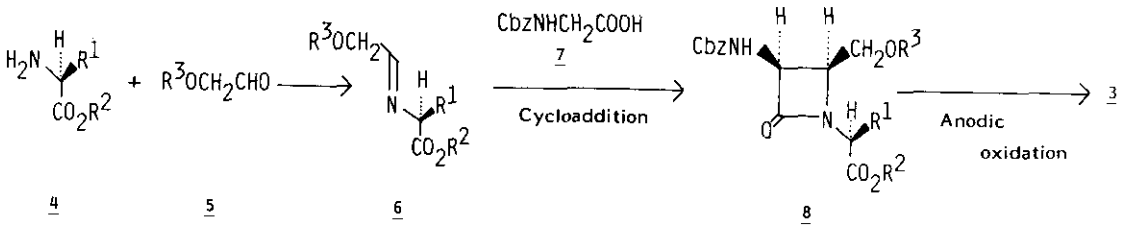


Chart 1

Cycloaddition of Cbz-Gly (**7**) with the Chiral Imines (**11a,b**)

Taking into consideration that the asymmetric cycloaddition of chiral cinnamylimines derived from L- and D-amino acids with phthalimidoacetyl and azidoacetyl chloride afforded chiral *cis*-β-lactams with moderate to high diastereoselectivity,[5] we investigated the cycloaddition of the imine (**11a,b**), derived from L-valine methyl ester and the *O*-substituted hydroxyacetaldehyde (**10a,b**), with a Cbz-Gly derivative. Two aldehydes, benzoyloxyacetaldehyde (**10a**)[6] and *p*-chlorobenzoyloxyacetaldehyde (**10b**), which possess the suitable functionality[7] for the 4-substituent of **3**, were prepared from Solketal (**9**) by a sequence of reactions involving: a) benzoylation or *p*-chlorobenzoylation, b) hydrolysis of the acetonide with *p*-toluenesulfonic acid, and c) periodide oxidation. Condensation of **10a,b** with L-valine methyl ester in the presence of $MgSO_4$ afforded the chiral imines (**11a,b**), which were used for the cycloaddition without purification (Chart 2).

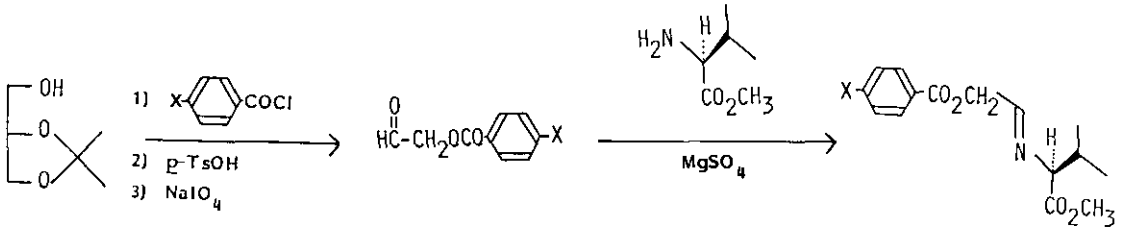


Chart 2 a : X=H b : X=Cl

The cycloaddition of the mixed anhydride[8] derived from Cbz-Gly and ethyl chloroformate with the imine (**11a**) was found to proceed smoothly at *room temperature*, and the desired *cis*-β-lactam (**12**) was obtained in 35% yield. When isobutyl chloroformate was used in place of ethyl chloroformate,[10] the yield was improved to 43%. The *cis*-β-lactam (**12**) thus obtained was deduced to be a mixture of the two diastereomers by means of the NMR spectrum, and various attempts to isolate the desired (3*S*,4*S*)-isomer from the mixture in a crystalline form were unsuccessful. Therefore, the imine (**11b**) was examined to obtain the β-lactam in a crystalline form. The cycloaddition of **11b** with the mixed anhydride prepared from Cbz-Gly and isobutyl

chloroformate, followed by fractional crystallization of the crude product afforded the desired (3*S*,4*S*)-β-lactam (**13**) in 20% overall yield from **10b**. The yield was slightly improved when isopropyl chloroformate was used in place of isobutyl chloroformate. The (3*R*,4*R*)-isomer (**14**) was also obtained as crystals from the mother liquor by further purification. The absolute configuration of **13** and **14** was determined by converting **13** into **3** (*vide infra*). The ratio of the two diastereomers (**13**:**14**) in the cycloaddition employing isopropyl chloroformate was 47:53 by HPLC analysis and the total conversion of **10b** into **13** and **14** was 82% (Chart 3). The lack of diastereoselectivity in this cycloaddition may be ascribed to the rather high reaction temperature required for the reaction to take place; a lower temperature (below 0°C) may be necessary to keep a rigid conformation in the transition state to realize high diastereoselectivity.

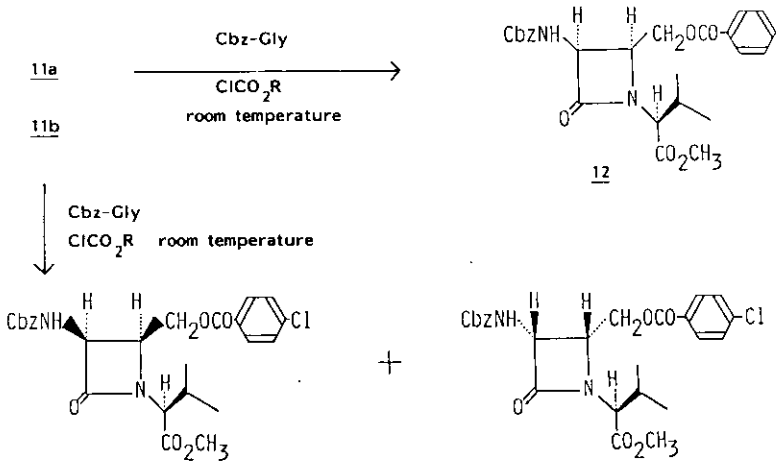
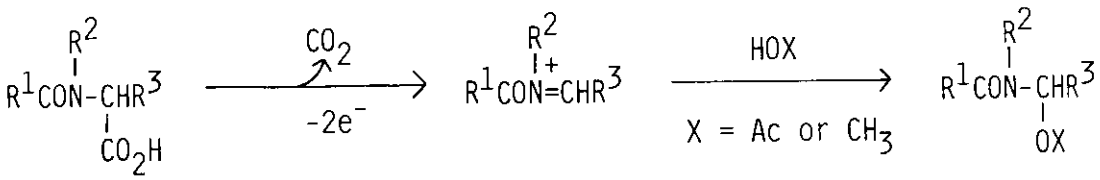


Chart 3

Removal of the N_1-Substituent in the β-Lactams by Anodic Oxidation

A method to remove N_1-substituents of some β-lactams arising from α-amino acids by decarboxylative oxidation with $Pb(OAc)_4$-$Cu(OAc)_2$ has been reported.[11] However, the use of reagents containing heavy metals appears to be undesirable in a large scale preparation. Since *N*-acylamino acids (**15**) are converted into the amidocarbinol derivatives (**17**) *via* the *N*-acyliminium salts (**16**) by anodic oxidation (Chart 4),[12] we tried to apply the electrochemical method to remove the N_1-substituents.



15 16 17

Chart 4

Conditions for the removal were investigated using the diastereomeric mixture (**12**). Hydrolysis of **12** with aqueous NaOH afforded the hydroxy acid (**18**), which was converted into the carbamoyloxymethyl derivative (**19**) by treatment with dichlorophosphoryl isocyanate followed by treatment with aqueous $NaHCO_3$. The anodic oxidation of the resulting two carboxylic acids (**18** and **19**) was carried out in acetic acid containing triethylamine using a platinum anode-platinum cathode in a nondivided cell to give the acetates **20a** and **21a**, respectively. The subsequent hydrolysis of these compounds with aqueous K_2CO_3 afforded the N_1-unsubstituted β-lactams, **22** (40% yield from **18**) and **23** (51% yield from **19**), respectively (Method 1). On the other hand, when the anodic oxidation of the acids (**18** and **19**) was carried out in methanol containing sodium methoxide using a graphite anode-graphite cathode in a nondivided cell, the amidoacetals **20b** and **21b** were obtained respectively. The subsequent acid hydrolysis of these compounds afforded the N_1-unsubstituted β-lactams, **22** (32% yield from **18**) and **23** (38% yield from **19**), respectively (Method 2) (Chart 5).

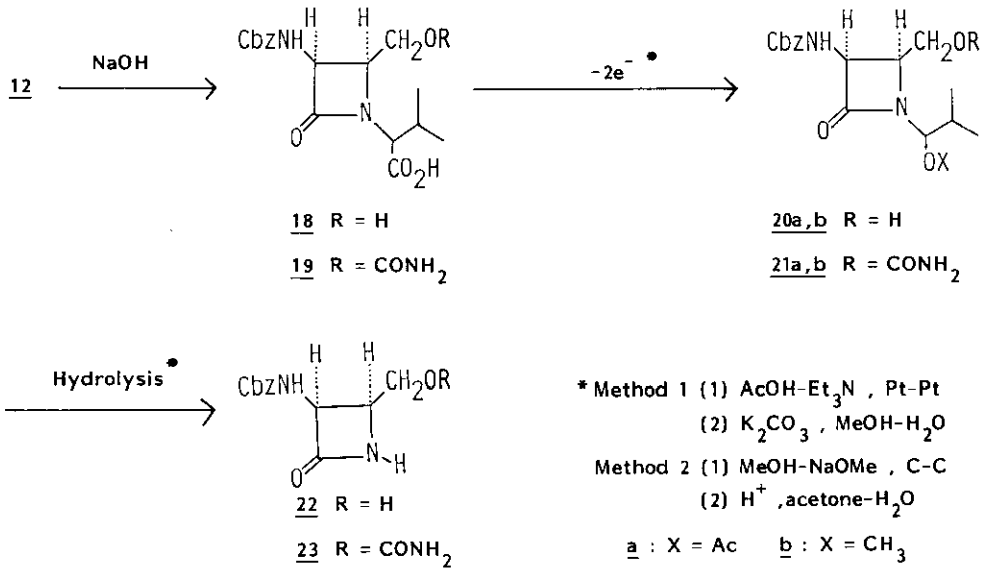


Chart 5

Application of this electrochemical method to the optically active β-lactams (**24** and **25**) afforded the chiral N_1-unsubstituted β-lactams (**3** and **26**) (Chart 6). Thus the β-lactam (**13**) was converted into the hydroxymethyl derivative (**24**) and the carbamoyloxymethyl derivative (**25**) in a similar manner to that used for converting **12** into **18** and **19**. The N_1-substituent of these β-lactams (**24** and **25**) was removed by Method 1 to give **26** and **3** in 37% and 41% overall yield from **13**, respectively. The N_1-unsubstituted β-lactam (**3**) obtained by this procedure was identical with the authentic sample of **3**.[2f,4] The 4-hydroxymethyl compound (**26**) proved to be useful as a chiral precursor for synthesizing a variety of sulfazecin-type compounds.[2f]

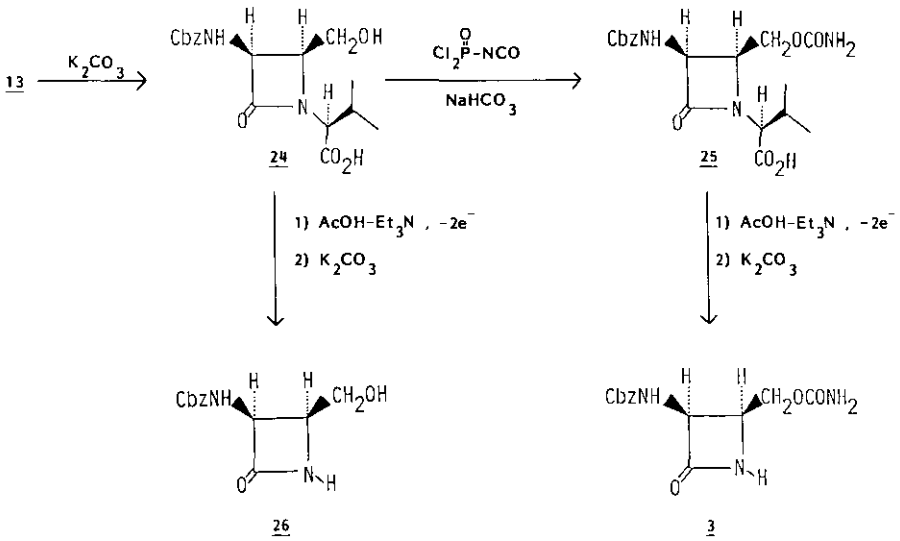


Chart 6

In summary, an alternative synthesis of a key intermediate (3) for preparing carumonam was achieved. The methods described here, especially the cycloaddition of Cbz-Gly *via* mixed anhydrides, and the anodic oxidative removal of the N_1-substituent may provide another development in β-lactam chemistry.

EXPERIMENTAL

Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a Hitachi 215 spectrophotometer, and mass spectra (MS) with a Hitachi RMU-60 mass spectrometer. ^{1}H-Nuclear magnetic resonance (NMR) spectra were taken on a Varian EM-390 (90 Mz) spectrometer with tetramethylsilane as an internal standard. Abbreviations are as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; br, broad; br.s, broad singlet. The optical rotations were recorded with a JASCO DPI-181 digital polarimeter.

Benzoyloxyacetaldehyde (10a)

A solution of benzoyl chloride (21.1 g, 0.15 mol) in dry CH_2Cl_2 (50 ml) was added dropwise to a solution of Solketal (9) (19.8 g, 0.15 mol) and pyridine (11.9 g, 0.15 mol) in dry CH_2Cl_2 (200 ml) at 5°C. The mixture was stirred for 2.5 h at 5°C, and water (50 ml) and AcOEt (50 ml) were added to the mixture. The organic phase was separated, washed with aq. $NaHCO_3$ and then with water, dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed on silica gel using hexane-toluene-AcOEt (4:2:1) as eluent to give 4-*benzoyloxymethyl*-2,2-*dimethyl*-1,3-*dioxolane* as a pale yellow oil, which was further purified by distillation (17.6 g, 73%, 125-128°C/2 mmHg).

The distillate (17.6 g, 74.6 mmol) was dissolved in a mixture of THF (100 ml) and water (40 ml). To the solution was added *p*-toluenesulfonic acid monohydrate (800 mg) and the mixture was refluxed for 3 h. The

pH of the mixture was adjusted to 7.5 with aq. $NaHCO_3$. Then, a solution of $NaIO_4$ (16.7 g, 78.2 mmol) in water (100 ml) was added to the mixture at 25°C, and the mixture was stirred for 2 h. The resulting precipitates were filtered off and the filtrate was evaporated to dryness. The residue was dissolved in AcOEt, and the solution was washed with brine, dried ($MgSO_4$) and evaporated. The residue was distilled to give benzoyloxyacetaldehyde (**10a**) (9.64 g, 79%, 85-88°C/2 mmHg).

Anal. Calcd for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.61; H, 4.81. IR (Neat) cm^{-1}: 3450, 1720, 1600, 1445, 1265. ^{1}H-NMR ($CDCl_3$) δ: 4.85 (2H, s, -OCH_2-), 7.10-7.86 and 8.02-8.27 (5H, m, aryl), 9.86 (1H, s, -CHO).

p-Chlorobenzoyloxyacetaldehyde (**10b**)

A solution of *p*-chlorobenzoyl chloride (25.1 g, 0.144 mol) in dry CH_2Cl_2 (50 ml) was added dropwise to a solution of Solketal (19.0 g, 0.144 mol) and pyridine (11.4 g, 0.144 mol) in dry CH_2Cl_2 (150 ml) at 5°C. The mixture was stirred for 2 h at 25°C and water (50 ml) was added to the mixture. The organic phase was separated, washed successively with 1N HCl, water, aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to dryness. Hexane (100 ml) was added to the residue. The insoluble precipitates were filtered off and the filtrate was evaporated. The residue was dissolved in a mixture of THF (390 ml) and water (130 ml). To the mixture was added *p*-toluenesulfonic acid monohydrate (2.93 g). The resulting solution was refluxed for 5 h. After most of the THF was evaporated under reduced pressure, water (100 ml) was added to the concentrate. The resulting aqueous solution was extracted with AcOEt. The extracts were washed with aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to dryness. AcOEt was added to the residue. The resulting insoluble precipitates were filtered off and the filtrate was evaporated. The residue was treated with hexane to give 1-(*p*-chlorobenzoyl)glycerine (16.2 g, mp 87-90°C, lit.[13] mp 89.5-90.5°C) as colorless crystals, which were dissolved in a mixture of THF (210 ml) and water (70 ml). To this solution was added a solution of $NaIO_4$(15.7 g, 73.5 mmol) in water (140 ml) at 5°C and the mixture was stirred for 4 h at 25°C. A solution of $NaIO_4$ (0.78 g) in water (5 ml) was further added to the mixture. After the mixture was stirred for an additional 2 h, most of the THF was evaporated under reduced pressure and brine (100 ml) was added to the residue. The resulting aqueous solution was extracted with AcOEt. The extracts were washed with brine, dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on silica gel with hexane-AcOEt (1:1) as eluent to give *p*-chlorobenzoyloxyacetaldehyde (**10b**) as a pale yellow oil, which was further purified by distillation (10.7 g, 77% bp 126°C/0.9 mmHg). The distillate crystallized on standing (mp 34-37°C).

Anal. Calcd for $C_9H_7ClO_3$: C, 54.43; H, 3.55. Found: C, 54.28; H, 3.43. IR (Nujol) cm^{-1}: 3450, 3100, 2940, 2870, 1720, 1595. ^{1}H-NMR ($CDCl_3$) δ: 4.88 (2H, s, -CH_2-), 7.40 (2H, d, J=9 Hz, aryl), 8.05 (2H, d, J=9 Hz, aryl), 9.75 (1H, s, CHO).

3,4-*cis*-4-Benzoyloxymethyl-3-benzyloxycarbonylamino-1-[(1*S*)-1-methoxycarbonyl-2-methylpropyl]-2-azetidinone (**12**)

L-Valine methyl ester hydrochloride (9.13 g, 54.5 mmol) and $NaHCO_3$ (6.86 g, 81.7 mmol) were dissolved in water (80 ml) at 25°C. The mixture was extracted with CH_2Cl_2, and the extracts were dried (Na_2SO_4). To this solution was added **10a** (8.49 g, 54.5 mmol) at 5°C, and the mixture was stirred for 30 min at the same temperature. $MgSO_4$ (5.44 g) was added to the mixture and the stirring was continued for an additional 1 h at 25°C. *$MgSO_4$ was filtered off and triethylamine (6.61 g, 65.4 mmol) was added to the filtrate. The solution* containing the imine (**11a**) was used for the subsequent reaction without purification.

Isobutyl chloroformate (44.3 g, 0.327 mol) was added to a solution of Cbz-Gly (22.7 g, 0.109 mmol) and triethylamine (33.1 g, 0.327 mol) in dry CH_2Cl_2 (350 ml) at -40°C. After the mixture was stirred for 5 min at -40°C, the imine (**11a**) solution described above was added to the mixture. The resulting mixture was warmed to 25°C rapidly, stirred for 16 h at 25°C, washed successively with water, 3N HCl, aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to dryness. The residue was subjected to column chromatography on silica gel. Gradient elution with hexane-AcOEt (3:1 → 5:3) gave **12** (10.8 g, 43%) as a viscous oil.

Mass (m/z): 468 (M^+). IR (Neat) cm^{-1}: 3350, 2975, 1770-1705 (br), 1455, 1280, 1205, 1120. ^{1}H-NMR ($CDCl_3$) δ: 0.76-1.10 (6H, m, $-CH_3$), 2.00-2.60 (1H, m, -CH<), 3.57 and 3.36 (3H, s x 2, $-OCH_3$), 3.90-3.20 (1H, m, $-CHCO_2-$), 4.20-4.45 (1H, m, C_4-H), 4.51-4.71 (2H, m, $-CH_2O-$), 5.03 (2H, s, $-OCH_2Ph$), 5.01-5.47 (1H, m, C_3-H), 5.90 and 6.03 (1H, d x 2, J = 9 Hz, -CONH-), 7.29 (5H, s, aryl), 7.12-7.70 and 7.95-8.20 (4H, m, aryl).

(3*S*,4*S*)-3-Benzyloxycarbonylamino-4-(*p*-chlorobenzoyloxymethyl)-1-[(1*S*)-1-methoxycarbonyl-2-methylpropyl]-2-azetidinone (**13**) and Its (3*R*,4*R*)-isomer (**14**)

Cycloaddition of the mixed anhydride prepared from Cbz-Gly (8.37 g, 40 mmol) and isopropyl chloroformate (14.7 g, 0.12 mol) with the imine (**11b**) prepared from **10b** (3.97 g, 20 mmol) and L-valine methyl ester hydrochloride (3.53 g, 20 mmol), was carried out in a similar manner to that described for the preparation of **12**. *The crude product was crystallized from isopropyl ether to give the* (3*S*,4*S*)-isomer (**13**, 2.65 g, 26%) as colorless crystals, mp 117-118°C. The mother liquor was concentrated under reduced pressure. The residue was chromatographed on silica gel with hexane-AcOEt (2:1) as eluent, to afford a white powder. The powder was further purified by recrystallization from isopropyl ether to give the (3*R*,4*R*)-isomer (**14**) as colorless crystals, mp 113-114°C.

On the other hand, when the crude product of the cycloaddition was subjected to column chromatography on silica gel with hexane-AcOEt as eluent (5:2 → 2:1), the diastereomeric mixture of **13** and **14** (8.26 g, 82%) were obtained as a white powder. The ratio was determined to be 47:53 by high performance liquid chromatographic analysis using Zorbax-CN (25 cm x 4.6 mm) with hexane-AcOEt (5:1) as the mobile phase.

13 : Anal. Calcd for $C_{25}H_{27}ClN_2O_7$: C, 59.70; H, 5.41; N, 5.57. Found: C, 59.40; H, 5.12; N, 5.60. $[\alpha]_D^{22}$ = -60.6° (c = 0.95, AcOEt). IR (KBr) cm^{-1} : 3320, 1765, 1735, 1725, 1690, 1525, 1275. ^{1}H-NMR ($CDCl_3$) δ : 0.93 and 1.02 (3H x 2, d x 2, J = 6 Hz, $-CH_3$), 2.10-2.60 (1H, m, -CH<), 3.60 (3H, s, $-OCH_3$), 4.09 (1H, d, J = 9 Hz, $-CHCO_2-$), 4.12-4.50 (1H, m, C_4-H), 4.50-4.80 (1H, m, $-OCH_2-$), 5.04 (2H, s, $-OCH_2Ph$), 5.30 (1H, dd, J = 5 and 10 Hz, C_3-H), 5.50 (1H, d, J = 10 Hz, -CONH-), 7.30 (5H, s, aryl), 7.40 and 7.90 (2H x 2, d x 2, J = 9 Hz, aryl).

14 : Anal. Calcd for $C_{25}H_{27}ClN_2O_7$: C, 59.70; H, 5.41; N, 5.57. Found: C, 59.63; H, 5.24; N, 5.51. $[\alpha]_D^{22}$ = +17.0° (c=0.735, AcOEt). IR (KBr) cm^{-1} : 3330, 1765, 1735, 1535, 1290, 1280, 1255. ^{1}H-NMR ($CDCl_3$) δ : 0.92 and 1.00 (3H x 2, d x 2, J=8 Hz, $-CH_3$), 2.00-2.50 (1H, m, -CH<), 3.66 (3H, s, $-OCH_3$), 3.98 (1H, d, J=10 Hz, $-CHCO_2-$), 4.20-4.45 (1H, m, C_4-H), 4.48-4.80 (2H, m, $-OCH_2-$), 5.04 (2H, s, $-OCH_2Ph$), 5.22 (1H, dd, J=5 and 9 Hz, C_3-H), 5.55 (1H, d, J=9 Hz, -CONH-), 7.30 (5H, s, aryl), 7.40 and 7.94 (2H x 2, d x 2, J=9 Hz, aryl).

3,4-*cis*-3-Benzyloxycarbonylamino-1-(1-carboxy-2-methylpropyl)-4-hydroxymethyl-2-azetidinone (18)

To a solution of **12** (8.14 g, 17.3 mmol) in THF (35 ml) and methanol (35 ml) was added dropwise 1N NaOH (34.8 ml) at 5 °C. The mixture was stirred for 30 min at 5°C and most of the methanol was evaporated under reduced pressure. The resulting aqueous solution was washed with ether, acidified to pH 1 with 3N HCl, and extracted with AcOEt. The extracts were washed with brine, dried ($MgSO_4$), and evaporated to dryness. The residue crystallized on standing in a refrigerator. Treatment of the crystals with ether afforded **18** (4.0 g, 66%) as colorless crystals. Recrystallization from AcOEt provided an analytical sample, mp 127-130°C.

Anal. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.13; H, 6.51; N, 7.91. IR (KBr) cm^{-1}: 3330, 2970, 1770, 1715, 1695, 1535, 1265, 1220, 1055. ^{1}H-NMR ($CDCl_3$) δ : 1.01 and 1.00 (3H x 2, d x 2, J=7 Hz, $-CH_3$), 1.95-2.55 (1H, m -CH<), 3.48-4.19 (3H, m, $-CH_2O-$ and C_4-H), 4.40 (1H, d, J=7 Hz, $-CHCO_2-$), 5.13 (2H, s, $-OCH_2Ph$), 5.30 (1H, dd, J=5 and 10 Hz, C_3-H), 5.90-6.49 (3 H, m, -OH and -CONH-), 7.38 (5H, s, aryl).

3,4-*cis*-3-Benzyloxycarbonylamino-4-carbamoyloxymethyl-1-(1-carboxy-2-methylpropyl)-2-azetidinone (19)

Dichlorophosphoryl isocyanate (1.19 g, 7.46 mmol) was added dropwise to a solution of **18**, prepared from **12** (2.33 g, 4.97 mmol) by the above method, in dry THF (20 ml) at 5°C. Then, aq. $NaHCO_3$ (25 ml) was added to the mixture, which was then stirred at 50°C for 3 h, and the pH was maintained between 4 and 5 with aq. $NaHCO_3$ during the reaction. The mixture was acidified to pH 1 with 3N HCl, and extracted with AcOEt. The extracts were washed with brine, dried ($MgSO_4$) and evaporated to dryness. The residue was treated with AcOEt and ether to give **19** (520 mg, 27%) as colorless crystals (mp 172-175°C). Although the mother liquor still contained **19**, further isolation was not attempted.

Anal. Calcd for $C_{18}H_{23}N_3O_7$: C, 54.46; H, 5.94; N, 10.58. Found: C, 54.32; H, 5.79; N, 10.65. IR (KBr) cm^{-1} : 3420, 3320, 2975, 1765, 1720, 1535, 1420, 1340, 1250. ^{1}H-NMR (d_6-DMSO) δ : 0.90 and 0.99 (3H x 2, d x 2, J=5 Hz, $-CH_3$), 3.01-3.54 (1H, br, $-CO_2H$), 3.68 (1H, d, J=9 Hz, $-CHCO_2-$), 3.73-4.05 (1H, m, C_4-H), 4.11 (2H, d, J=5 Hz, $-CH_2O-$), 4.94 (1H, dd, J=6 and 9 Hz, C_3-H), 5.04 (2H, s, $-OCH_2Ph$), 6.28-6.60 (2H, br.s, $-NH_2$), 7.31 (5H, s, aryl), 7.98 (1H, d, J=9 Hz, -CONH-).

3,4-*cis*-3-Benzyloxycarbonylamino-4-hydroxymethyl-2-azetidione (22)

Method 1

Anodic oxidation of **18** (700 mg, 2 mmol) was carried out in acetic acid containing triethylamine (4 ml) using a platinum anode-platinum cathode in a nondivided cell at 20-30°C. The end point of the reaction was detected by thin layer chromatography. AcOEt was added to the mixture, which was then washed

successively with water, saturated aq. $NaHCO_3$ (120 ml x 3), and brine, dried ($MgSO_4$), and evaporated to dryness. The residue was dissolved in methanol (40 ml). To the solution was added dropwise a solution of K_2CO_3 (276 mg, 2 mmol) in water (10 ml) at 5°C. The mixture was stirred for 1 h at 5°C, and most of the methanol was evaporated under reduced pressure. The residue was extracted with AcOEt. The extracts were washed successively with water, 3N HCl and brine, dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed on silica gel with AcOEt-methanol (10:1) as eluent to give **22** (200 mg, 40%) as colorless crystals, mp 102-104°C (lit.[20] mp 103-104°C).

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found : C, 57.30; H, 5.60; N, 10.95.

Method 2

Anodic oxidation of **18**, prepared from **12** (2.71 g, 5.78 mmol) by the above method, was carried out in methanol containing sodium methoxide (30 mg) using a graphite anode-graphite cathode in a nondivided cell at 5-15°C. The end point of the reaction was detected by thin layer chromatography. Most of the methanol was evaporated under reduced pressure. AcOEt and water were added to the mixture. The organic phase was separated and washed successively with aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to dryness. The residue was dissolved in a mixture of acetone (20 ml) and water (10 ml). To the solution was added methanesulfonic acid (0.2 ml), and the resulting mixture was refluxed for 6 h. The mixture was extracted with AcOEt. The extracts were washed successively with aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed on silica gel with AcOEt-methanol (10:1) as eluent to give **22** (460 mg, 32%) as colorless crystals, mp 102-104°C (lit.[20] mp 103-104°C).

Anal. Calcd for $C_{12}H_{14}N_2O_4 \cdot 1/5H_2O$: C, 56.78; H, 5.72; N, 11.04. Found: C, 56.62; H, 5.71; N, 10.87.

3,4-*cis*-3-Benzyloxycarbonylamino-4-carbamoyloxymethyl-2-azetidinone (**23**)

Method 1

Anodic oxidation of **19** (393 mg, 1 mmol) was carried out in a similar manner to that described for the preparation of **22** (Method 1) to give **23** (150 mg, 51%) as colorless crystals, mp 208-210 °C (lit.[20] mp 210-211°C).

Anal. Calcd for $C_{13}H_{15}N_3O_5$: C, 53.24; H, 5.15; N, 14.33. Found: C, 53.07; H, 5.09; N, 14.22.

Method 2

Anodic oxidation of **19** (393 mg, 1 mmol) was carried out in a similar manner to that described for the preparation of **22** (Method 2) to give **23** (120 mg, 38%) as colorless crystals, mp 208-210 °C (lit.[20] mp 210-211°C).

Anal. Calcd for $C_{13}H_{15}N_3O_5 \cdot 3/10H_2O$: C, 52.28; H, 5.26; N, 14.07. Found: C, 52.44; H, 5.15; N, 13.76.

(3*S*,4*S*)-3-Benzyloxycarbonylamino-4-hydroxymethyl-2-azetidinone (**26**)

A solution of K_2CO_3 (995 mg, 7.2 mmol) in water (10 ml) was added dropwise to a solution of **13** (1.51 g, 3 mmol) in methanol (20 ml) at 5°C. The mixture was stirred for 12 h at 25°C. Most of the methanol was evaporated under reduced pressure. The residual solution was washed with ether and acidified to pH 1 with 3N HCl. The mixture was extracted with AcOEt. The extracts were washed with brine, dried ($MgSO_4$) and evaporated to dryness to give (3*S*,4*S*)-3-benzyloxycarbonylamino-1-[(1*S*)-1-carboxy-1-methylpropyl]-4-hydroxymethyl-2-azetidinone (**24**) as an oil, which was used without further purification. Anodic oxidation of **24** was carried out in a similar manner to that described for the preparation of **22** (Method 1). The crude product was chromatographed on silica gel with AcOEt-methanol (10:1) as eluent to give **26** (280 mg, 37%) as colorless crystals, mp 127-129°C.

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.57; H, 5.62; N, 11.00. IR (KBr) cm^{-1}: 3400, 3280, 1750-1700, 1550, 1270, 1070. $[\alpha]_D^{24} = +22.9°$ (c=0.245, MeOH).

(3*S*,4*S*)-3-Benzyloxycarbonylamino-4-carbamoyloxymethyl-2-azetidinone (**3**)

The azetidinone (**24**), prepared from **13** (1.6 g, 3.18 mmol), was converted into **25** in a similar manner to that described for the preparation of **19**. Anodic oxidation of **25** was carried out in a similar manner to that described for the preparation of **22** (Method 1) to give **3** (380 mg, 41%) as colorless crystals, mp 191-193°C (lit.[4] mp 193-195°C).

Anal. Calcd for $C_{13}H_{15}N_3O_5$: C, 53.24; H, 5.15; N, 14.33. Found: C, 53.04; H, 5.23; N, 14.20. $[\alpha]_D^{21} = +61.0°$ (c=0.2, MeOH). {lit.[20] $[\alpha]_D^{25} = +60.6°$ (MeOH) lit.[4] $[\alpha]_D^{20} = +61.2°$ (MeOH)}.

ACKNOWLEDGEMENT

The authors wish to thank Dr. K. Morita of this Division for his encouragement throughout this work.

REFERENCES

1) A part of this work was presented at the 106th Annual Meeting of Pharmaceutical Society of Japan, Chiba, April, 1986.

2) a) S. Kishimoto, M. Sendai, S. Hashiguchi, M. Tomimoto, Y. Satoh, T. Matsuo, M. Kondo, and M. Ochiai, *J. Antibiot.*, 1983, **36**, 1421.

b) T. Matsuo, T. Sugawara, H. Masuya, Y. Kawano, N. Noguchi, and M. Ochiai, *Chem. Pharm. Bull.*, 1983, **31**, 1874.

c) T. Matsuo, H. Masuya, T. Sugawara, Y. Kawano, N. Noguchi, and M.Ochiai, *Chem. Pharm. Bull.*, 1983, **31**, 2200.

d) S. Kishimoto, M. Sendai, M. Tomimoto, S. Hashiguchi, T. Matsuo, and M. Ochiai, *Chem. Pharm. Bull.*, 1984, **32**, 2646.

e) K. Yoshioka, T. Miyawaki, S. Kishimoto, T. Matsuo, and M. Ochiai, *J. Org. Chem.*, 1984, **49**, 1427.

f) M. Sendai, S. Hashiguchi, M. Tomimoto, S. Kishimoto, T. Matsuo, M. Kondo, and M. Ochiai, *J. Antibiot.*, 1985, **38**, 346.

g) N. Noguchi, H. Masuya, T. Sugawara, Y. Kawano, T. Matsuo, and M. Ochiai, *J. Antibiot.*, 1985, **38**, 1387.

h) M. Sendai, S. Hashiguchi, M. Tomimoto, S. Kishimoto, T. Matsuo, and M. Ochiai, *Chem. Pharm. Bull.*, 1985, **33**, 3798.

3) A. Imada, K. Kintaka, K. Kitano, M. Muroi, and M. Asai, *Nature*, 1981, **289**, 590.

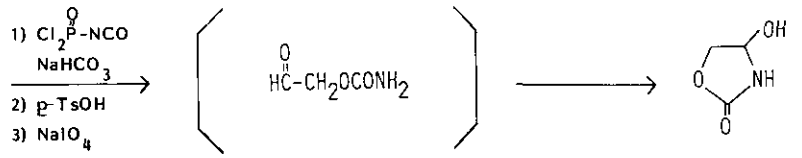
4) C. Hubschwerlen and G. Schmit, *Japan Provisional Patent Publication*, 58-46066.

5) a) S. M. Tenneson and B. Belleau, *Can. J. Chem.*, 1980, **58**, 1605.

b) T. Sugawara, Y. Kawano, and K. Yoshioka, *Japan Provisional Patent Publication*, 60-112757.

6) S. Aoyama, *Yakugaku Zasshi*, 1927, 9.

7) Although carbamoyloxyacetaldehyde (**27**) was first prepared as a direct precursor according to the following scheme, **27** was not used for the subsequent reaction, because of its easy cyclization to **28**.



9 **27** **28**

8) Although cycloaddition of acid chloride of Cbz-Gly with a benzimine has been briefly reported,[9] an attempted reaction with the imine (**10a**) under similar conditions afforded the β-lactam (**12**) only in a poor yield.

9) A. K. Bose, H. P. S. Chawla, S. Dayal, and M. S. Manhas, *Tetrahedron Lett.*, 1973, 2503.

10) E. Schröder and K. Lübke, 'The Peptides, Vol. 1, Methods of Peptide Synthesis' Academic Press, New York and London, 1965, p. 85.

11) A. K. Bose, M. Tsai, S. D. Sharma, and S. M. Manhas, *Tetrahedron Lett.*, 1973, 3851.

12) a) T. Iwasaki, H. Horikawa, K. Matsumoto, and M. Miyoshi, *J. Org. Chem.*, 1977, **42**, 2419.

b) H. Horikawa, T. Iwasaki, K. Matsumoto, and M. Miyoshi, *J. Org. Chem.*, 1978, **43**, 355.

13) O. E. Von Louizen and P. E. Verkade, *Rec. Trav. Chem.*, 1959, **78**, 460.

Received, 28th April, 1986