# Synthesis of Novel Monobactams Bearing an (*R*)-1-Hydroxyethyl Group and an (*S*)-1-Carbamoyloxyethyl Group at the $C_{3,4}$-Positions

Kikoh OBI,[1] Yoshio ITO, and Shiro TERASHIMA*

*Sagami Chemical Research Center, 4–4–1 Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan.* *Received September 19, 1989*

**Various structural types of monobactams bearing an (*R*)-1-hydroxyethyl and an (*S*)-1-carbamoyloxyethyl group at the $C_{3,4}$-positions, respectively, could be synthesized from (3*S*,4*S*)-4-[(*S*)-1-benzyloxyethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone. These synthetic studies explored several novel methods applicable to construct substituted carbamoyloxy groups.**

**Keywords** monobactam; carbapenem; (*R*)-1-hydroxyethyl group; (*S*)-1-carbamoyloxyethyl group; (3*S*,4*S*)-4-[(*S*)-1-benzyloxyethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone; *p*-nitrophenyl carbonate; carbamoylation; sulfonation; 2-azetidinone-1-sulfonate; antibacterial activity

In 1981, the unique monocyclic $\beta$-lactam antibiotics classified afterwards as monobactams were independently discovered by research groups at Squibb[2] and Takeda.[3] Since then, numerous chemical modifications of those natural antibiotics have been studied extensively at the $C_3$-amido side chain and $C_4$-substituents,[4] culminating in the successful developments of aztreonam (**1**)[5] and carmonum (**2**)[6] at Squibb and Takeda, respectively. These novel monobactams (**1** and **2**) have already been brought into clinical use.

On the other hand, it is well known that the carbapenems represented by imipenem (**3**), which characteristically have an (*R*)-1-hydroxyethyl group at the $C_6$-position, exhibit prominent antibacterial activity as well as broad spectra.[7] As shown in Chart 1, we have recently succeeded in developing an efficient synthetic route to the carbapenem key intermediate (**4**) starting from (*S*)-ethyl lactate (**5**).[8] Our scheme features the highly stereoselective [2+2]-cycloaddition reaction of the imine (**6**) with diketene, and proceeds through the novel monocyclic $\beta$-lactam (**8**) carrying an (*R*)-1-hydroxyethyl group at the $C_3$-position.

Considering the availability of a large quantity of **8** and the prominent antibacterial properties of **1**—**3**, we designed the novel monobactams (**9**), which may be readily constructed from **8**.[9] We were very much interested in the antibacterial properties of **9** since they carry an (*R*)-1-hydroxyethyl and an (*S*)-1-carbamoyloxyethyl group at the $C_{3,4}$-positions, respectively, and their absolute configurations at the $C_{3,4}$-positions are identical with those of **3**.

We wish to report on the synthesis of various structural types of **9** which could be achieved by applying several novel methods to construct substituted carbamoyloxy groups.

## Results and Discussion

The syntheses of **9** commence with transposition of the protective groups involved in **8**, readily obtainable from **5**, according to the established reaction scheme.[8] As shown in Chart 2, in order to introduce a carbamoyl group into the $C_4$-side chain of **8**, the (*R*)-1-hydroxyethyl group present at

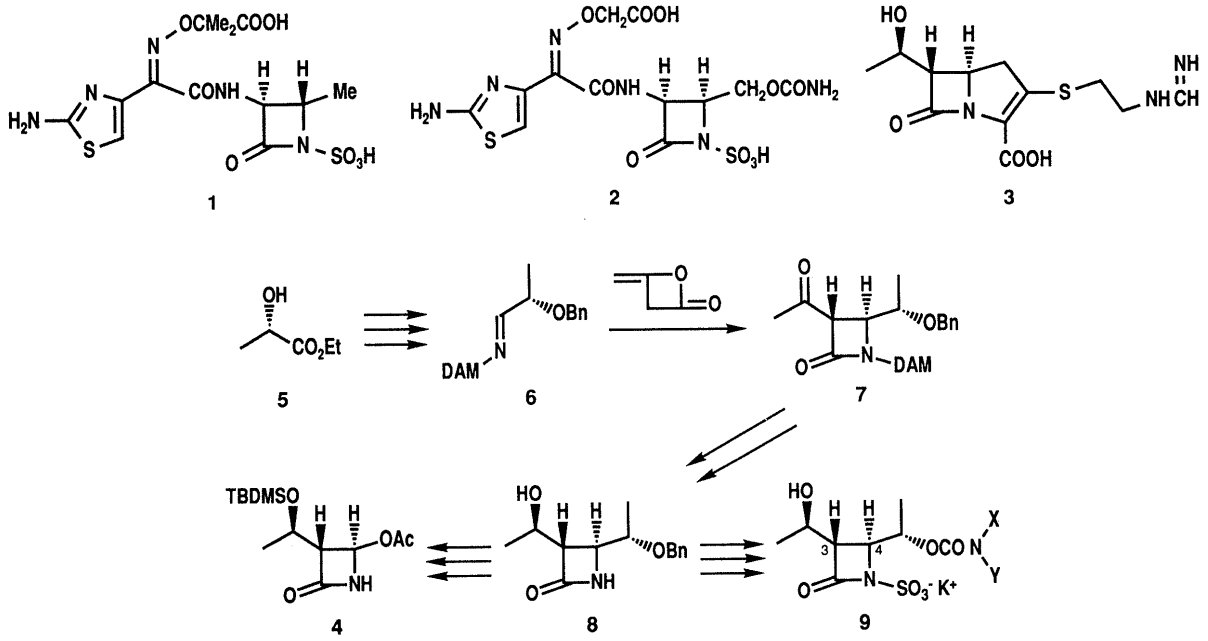
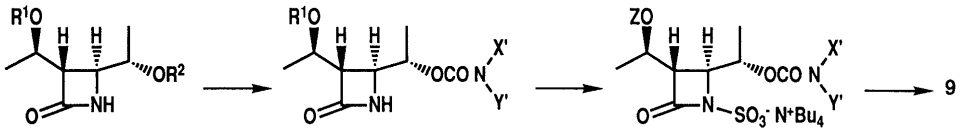



Chart 1



8: $R^1$=H, $R^2$=Bn
10: $R^1$=THP, $R^2$=Bn
11: $R^1$=THP, $R^2$=H
12: $R^1$=THP, $R^2$=$CO_2C_6H_4$-*p*-$NO_2$

13: $R^1$=THP
14: $R^1$=Z

15

a: X=X'=Y=Y'=H
b: X=X'=Me, Y=Y'=H
c: X=X'=Y=Y'=Me
d: X=$CH_2CO_2^-K^+$, X'=$CH_2CO_2$Bn, Y=Y'=H
e: X=$CH_2CO_2^-K^+$, X'=$CH_2CO_2$Bn, Y=Y'=Me
f: X,Y=-$(CH_2)_2NH(CH_2)_2$-, X',Y'=-$(CH_2)_2NZ(CH_2)_2$-,
g: X=X'=  Y=Y'=H
h: X=X'=  Y=Y'=H
i: X=-$(CH_2)_2$OH, X'=-$(CH_2)_2$OZ [for 13i, X'=-$(CH_2)_2$OH], Y=Y'=H
j: X=X'=-$C_6H_5$, Y=Y'=H
k: X=X'=-$C_6H_4$-*p*-F, Y=Y'=H

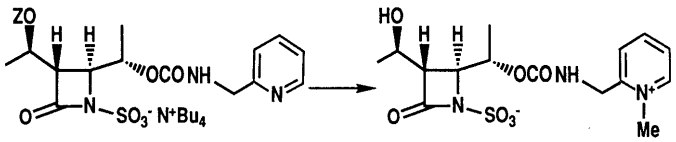
THP= 
Z=$CO_2CH_2C_6H_5$

Chart 2

the $C_3$-position was first protected in the form of a tetrahydropyran-2-yl (THP) ether in 98% yield. Subsequent hydrogenolysis of the benzyl ether of **10** afforded the 4-[(*S*)-1-hydroxyethyl]-2-azetidinone (**11**) in a quantitative yield. Treatment of **11** with *p*-nitrophenyl chloroformate in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) gave rise to the *p*-nitrophenyl carbonate (**12**), the key synthetic intermediate of **9**,[10] in 97% yield.

Reactions of **12** with excess amounts of ammonia, methylamine and dimethylamine in methanol room temperature cleanly produced the corresponding carbamates (**13a—c**) in 89—98% yields, respectively.[10] After removal of the THP groups of **13a—c**, the secondary alcohols formed were again protected with benzyloxycarbonyl chloride (Z–Cl) in the presence of DMAP, giving the carbamates (**14a—c**) in 58—71% yields. Sulfonation of **14a—c** with sulfur trioxide–pyridine complex ($SO_3$–Py)[5,6] followed by treatment with tetrabutylammoniun hydrogensulfate afforded the ammonium salts (**15a—c**) in 81—93% yields. These salts (**15a—c**) could be easily purified by column chromatography on silica gel. Reductive removal of the Z groups of **15a—c** and subsequent treatment with ion exchange resin [AG50W-X2($K^+$-form)] furnished the desired potassium salts of the monobactams (**9a—c**) in excellent yields.

Among **9a—c** so far obtained, only the monosubstituted carbamate derivative (**9b**) was found to exhibit marginal antibacterial activity (*vide infra*). Accordingly, further synthetic studies on **9** were attempted, mainly employing monosubstituted amines for the carbamate formation. Thus, novel monobactams (**9d—k**) could be prepared from **12** similarly to **9a—c** by using benzyl glycinate, benzyl *N*-methyl-glycinate,[11] 1-benzyloxycarbonylpiperazine,[12] 2-(aminomethyl)pyridine, cyclopropylamine, ethanolamine, aniline, and *p*-fluoroaniline as amine counterparts, respectively.[13] These compounds were employed as representative monosubstituted amines, which may cover a wide range of structural variations. In the syntheses of **9j,k**, heating of a mixture of **12** and aniline or *p*-fluoroaniline



15g 16

Chart 3

without solvent at 60 °C was necessary for carbamate formation because of the lower nucleophilicity of the aniline derivatives.

As shown in Chart 3, the ammonium salt (**15g**) obtained from **12** and 2-aminomethylpyridine by way of **13g** and **14g** was also derived to the intramolecular ammonium salt (**16**) by sequential hydrogenolysis and methylation. These two steps gave 80% and 93% yields, respectively.

Next, with the aim of obtaining **9** in which one of the two substituents of the carbamoyl group (X or Y) involves an oxygen functionality, the *N*-methoxy carbamate (**14l**) was synthesized from **12** and methoxyamine similarly to **14a—c**, as shown in Chart 4. Sulfonation of **14l** as done for **14a—c** was found to produce the mono- and the diammonium salts (**17** and **15l**) in 36% and 41% yields, respectively. The structures of these salts could be assigned at the stages of **18** and **91** based on the nuclear magnetic resonance (NMR) spectra.[14] This result clearly shows that the nitrogen atom of the *N*-methoxycarbamate moiety is more nucleophilic than that of the β-lactam ring. These ammonium salts (**17** and **15l**) were directly derived to the mono- and the dipotassium salts (**18** and **9l**) in the same manner as described for the syntheses of **9a—c**.[14]

In order to avoid the double sulfonation, preparation of the *N*-benzyl-*N*-alkoxycarbamates (**14m,n**) was next attempted. Toward this end, *N*-benzyl-methoxyamine[15] and *N*-benzyl-benzyloxyamine were subjected to the carbamate formation. Unexpectedly, these amines were found not to react with **12**. After experimentation, it was found that the desired protected carbamates (**14m, n**) could be effectively

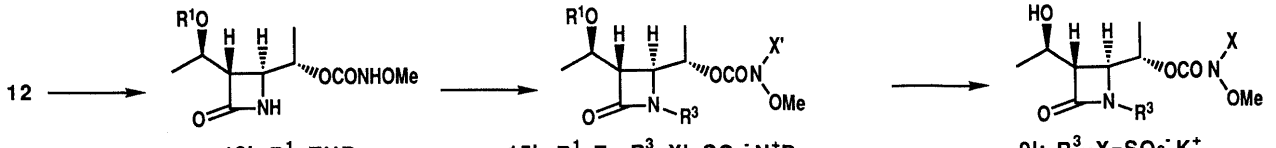



Chart 4

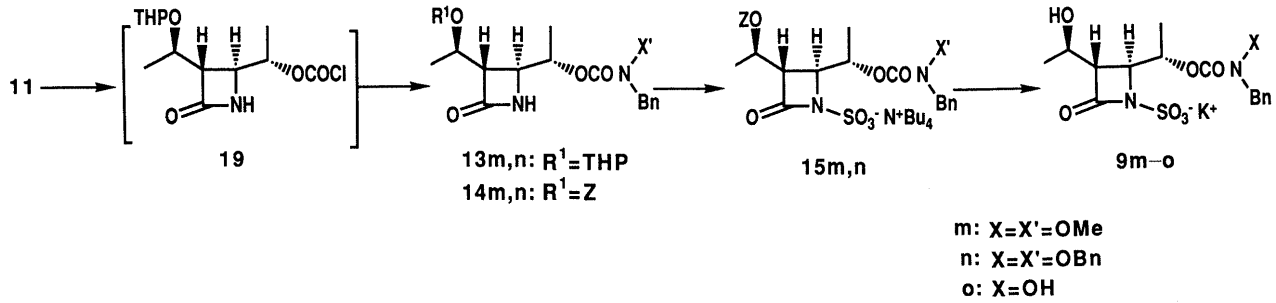



Chart 5

produced from **11** by way of the chloroformate (**19**). As shown in Chart 5, treatment of **11** with trichloromethyl chloroformate in pyridine gave rise to **19**,[16] which without isolation was allowed to react with the amine derivatives to yield **13m,n**. Sequential acidic removal of the THP groups and benzyloxycarbonylation gave **14m,n** in good combined yields from **11**. Similarly to **9a—c**, these compounds (**14m,n**) were derived to **9m,n**. Further hydrogenolysis of **9n** over 20% palladium on charcoal (Pd–C) under hydrogen at 2 atm pressure produced **9o** having an *N*-hydroxycarbamate moiety.[17] When **9m,n** were treated under more forcing conditions for hydrogenolysis, reductive removal of the sulfonate moieties preceded the desired cleavage of the *N*-benzyl groups.

As mentioned above, we have succeeded in preparing various structural types of optically active monobactams (**9a—o** and **16**) bearing an (*R*)-1-hydroxyethyl group and an (*S*)-1-carbamoyloxyethyl group at the $C_{3,4}$-positions. In the course of these synthetic studies employing **8** as a starting material, several novel methods applicable to the construction of substituted carbomoyloxy groups were developed. These novel monobactams (**9a—o** and **16**) were subjected to evaluation of *in vitro* antibacterial activity along with **18**. However, contrary to our expectation, only **9b** was found to possess a very weak antibacterial activity against *Escherichia coli* NIHJ (12.5 μg/ml)[18] and *Proteus mirabilis* IID994 (50 μg/ml).[18]

## Experimental

All melting points were determined with a Yamato MP-21 melting point apparatus and are uncorrected. Infrared (IR) spectral measurements were carried out with a JASCO A-202 diffraction grating infrared spectrometer. $^1$H-NMR spectra were measured with Hitachi R-90H (90 MHz) and Bruker AM spectrometers (400 MHz). All signals were expressed as ppm downfield from tetramethylsilane used as an internal standard (δ-value). Mass spectra (MS) were taken with a Hitachi RMU-6MG mass spectrometer and Hitachi M-80A mass spectrometer [secondary ion mass spectrometry (SIMS)]. Measurements of optical rotation were performed with a Horiba SEPA 200 automatic digital polarimeter. Wakogel C-300 was used as an adsorbent for column chromatography.

**(3*S*,4*S*)-4-[(*S*)-1-Benzyloxyethyl]-3-[(*R*)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (10)** A mixture of (3*S*,4*S*)-4-[(*S*)-1-benzyloxyethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone (**8**)[8] (1.00 g, 4.01 mmol), 3,4-dihydro-2*H*-pyran (1.83 ml, 20.1 nmol), and pyridinium *p*-toluenesulfonate (60 mg) in $CH_2Cl_2$ (10 ml) was stirred at room temperature for 2 h, and then diluted with $CH_2Cl_2$ (30 ml). The organic layer was washed successively with $H_2O$ and saturated NaCl, then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue, which was purified by column chromatography ($SiO_2$, hexane–AcOEt (7 : 3)) to give **8** as a colorless oil (1.31 g, 98%). IR (neat): 2950, 1760 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.24 (3H, d, $J$=5.9 Hz, $CH_3$), 1.33 (3H, d, $J$=6.4 Hz, $CH_3$), 1.47—1.73 (6H, m, $(CH_2)_3$), 2.77—2.85 (1H, m, $C_3$-H), 3.41—3.60 (4H, m, $C_4$-H, CHO-THP and $OCH_2$), 4.07 (1H, d q, $J$=each 6.4 Hz, CHO-Bn), 4.40 (1H, d, $J$=11.6 Hz, OCHPh), 4.68 (1H, d, $J$=11.6 Hz, OCHPh) 4.74 (1H, br s, OCHO), 6.07 (1H, br s, NH), 7.32 (5H, s, $C_6H_5$). MS *m/z*: 248 $(M-THP)^+$.

**(3*S*,4*S*)-3-[(*R*)-1-Tetrahydropyran-2-yloxyethyl]-4-[(*S*)-1-hydroxyethyl]-2-azetidinone (11)** A mixture of **10** (5.33 g, 16.0 mmol), 5% Pd–C (0.30 g) and 5 drops of 1 N HCl in tetrahydrofuran (THF) (30 ml) was stirred at room temperature for 5.5 h under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give **11** as a colorless oil (3.85 g, quantitative yield). IR (neat): 3300, 2950, 1740 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.25 (1.5H, d, $J$=6.2 Hz, $CH_3$CHO-THP), 1.27 (1.5H, d, $J$=6.2 Hz, $CH_3$CHO-THP), 1.35 (3H, d, $J$=6.8 Hz, $CH_3$CHOH), 1.41—1.80 (6H, m, $(CH_2)_3$), 2.93 (1H, dd, $J$=2.2, 5.5 Hz, $C_3$-H), 3.42—4.10 (5H, m, $C_4$-H, 2×CHO and $OCH_2$), 4.72 (1H, br s, OCHO), 6.17 (1H, br s, NH). MS *m/z*: 244 $(M+1)^+$, 142 $(M-THPO)^+$.

**(3*S*,4*S*)-3-[(*R*)-1-Tetrahydropyran-2-yloxyethyl]-4-[(*S*)-1-(*p*-nitrophenoxycarbonyloxy)ethyl]-2-azetidinone (12)** 4-Nitrophenyl chloroformate (4.78 g, 23.7 mmol) was added to a solution of **11** (3.85 g, 15.8 mmol) in pyridine (14 ml) at 0 °C under an argon atmosphere. After stirring at room temperature for 17 h, the mixture was diluted with AcOEt (250 ml). The ethyl acetate solution was washed successively with $H_2O$ and saturated NaCl, then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* followed by purification by column chromatography ($SiO_2$, $CH_2Cl_2$–AcOEt (3 : 1)) gave **12** as a pale yellow caramel (6.25 g, 97%). IR (neat): 2750, 1760, 1710, 1530, 1220 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.29 (1.5H, d, $J$=6.6 Hz, $CH_3$CHO-THP), 1.38 (1.5H, d, $J$=6.6 Hz, $CH_3$CHO-THP), 1.48 (1.5H, d, $J$=6.4 Hz, $CH_3$CHO), 1.62 (1.5H, d, $J$=6.4 Hz, $CH_3$CHO), 1.58—1.83 (6H, m, $(CH_2)_3$), 2.89—3.02 (1H, m, $C_3$-H), 3.42—3.56 (1H, m, $C_4$-H), 3.77—3.92 (2H, m, $OCH_2$), 4.13 (1H, dq, $J$=each 6.6 Hz, THP-OCH), 4.73 (1H, br s, OCHO), 4.87 (1H, dq, $J$=each 6.4 Hz, CHOCO), 6.24 (1H, br s, NH), 7.39, 8.29 (4H, two d, $J$=each 9.2 Hz, $C_6H_4$). MS *m/z*: 270 $(M-NO_2-C_6H_4O)^+$.

**(3*S*,4*S*)-4-[(*S*)-1-Carbamoyloxyethyl]-3-[(*R*)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (13a)** A 28% aqueous solution of ammonia (0.5 ml) was added to a solution of **12** (0.158 g, 0.39 mmol) in MeOH (2 ml). The reaction mixture was stirred at room temperature for 2 h, then concentrated *in vacuo* to give a residue, which was purified by column chromatography ($SiO_2$, hexane–AcOEt (3 : 7)) to give **13a** as a colorless oil (0.099 g, 89%). $^1$H-NMR ($CDCl_3$) δ: 1.23—1.84 (12H, m, 2×$CH_3$ and $(CH_2)_3$), 2.88—2.97 (1H, m, $C_3$-H), 3.49—3.87 (2H, m, $OCH_2$), 3.78 (1H, dd, $J$=2.2, 6.6 Hz, $C_4$-H), 3.98—4.24 (1H, m, THP-OCH), 4.71 (1H, br s, OCHO), 4.76 (1H, dq, $J$=each 6.6 Hz, CHOCO), 6.08 (1H, br s, NH). The

carbamates (**13b,c**) were prepared from **12** in a similar manner to that described above.

**(3*S*,4*S*)-4-[(*S*)-1-(*N*-Methylcarbamoyloxy)ethyl]-3-[(*R*)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (13b)** Prepared from **12** (0.433 g, 1.08 mmol) and a 40% aqueous solution of methylamine (2 ml) as a colorless oil (0.318 g, 98%). IR (neat): 3300, 2950, 1760, 1710, 1250 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.22 (12H, m, $2\times CH_3$ and $(CH_2)_3$), 2.79 (3H, d, $J$=4.8 Hz, N-$CH_3$), 2.89—2.99 (1H, m, $C_3$-H), 3.43—3.85 (2H, m, $OCH_2$), 3.70 (1H, dd, $J$=2.0, 6.6 Hz, $C_4$-H), 3.95—4.24 (1H, m, THP-OCH), 4.73 (2H, br s, NH and OCHO), 4.82 (1H, dq, $J$=each 6.6 Hz, CHOCO), 6.15 (1H, br s, NH and OCHO). MS $m/z$: 199 $(M-THPO)^+$.

**(3*S*,4*S*)-4-[(*S*)-1-(*N*,*N*-Dimethycarbamoyloxy)ethyl]-3-[(*R*)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (13c)** Prepared from **12** (0.970 g, 2.38 mmol) and a 40% aqueous solution of dimethylamine (8 ml) as a colorless oil (0.716 g, 96%). $^1$H-NMR ($CDCl_3$) $\delta$: 1.22—1.89 (12H, m, $2\times CH_3$ and $(CH_2)_3$), 2.90 (6H, s, $NMe_2$), 2.93 (1H, dd, $J$=2.2, 6.6 Hz, $C_3$-H), 3.68—3.86 (2H, m, $OCH_2$), 3.82 (1H, dd, $J$=2.2, 6.4 Hz, $C_4$-H), 4.06—4.24 (1H, m, THP-OCH), 4.74 (1H, br s, OCHO), 4.85 (1H, dq, $J$=each 6.4 Hz, CHOCO), 6.21 (1H, br s, NH).

**(3*S*,4*S*)-4-[(*S*)-1-(*N*-(Benzyloxycarbonylmethyl)carbamoyloxy)ethyl]-3-[(*R*)-1-tetrahydropyran-2-lyoxyethyl]-2-azetidinone (13d)** Triethylamine (0.22 ml, 1.57 mmol) was added to a mixture of **12** (0.536 g, 1.31 mmol) and the *p*-toluenesulfonic acid salt of benzyl glycinate (0.530 g, 1.57 mmol) in MeOH (5 ml) at 0 °C. The mixture was stirred at the same temperature for 0.5 h, then at room temperature for 3.5 h. Concentration of the mixture *in vacuo* followed by purification by column chromatography ($SiO_2$, hexane–AcOEt (7:3)) gave **13d** as a pale yellow oil (0.517 g, 91%). IR (neat): 3340, 1760, 1720, 1520, 1220 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.22—1.78 (12H, m, $2\times CH_3$ and $(CH_2)_3$), 2.86—2.94 (1H, m, $C_3$-H), 3.41—3.86 (3H, m, $C_4$-H and $OCH_2$), 3.98 (2H, d, $J$=5.7 Hz, $NCH_2COO$), 4.01—4.23 (1H, m, THP-OCH), 4.72 (1H, br s, OCHO), 4.82 (1H, dq, $J$=each 6.6 Hz, CHOCO), 5.18 (2H, s, $PhCH_2$), 5.34 (1H, br s, NH), 6.22 (1H, br s, NH), 7.35 (5H, s, $C_6H_5$). MS $m/z$: 349 $(M-THP)^+$, 333 $(M-THPO)^+$. The carbamates (**13e, l**) were prepared from **12** in a similar manner to that described above.

**(3*S*,4*S*)-4-[(*S*)-1-(*N*-Benzyloxycarbonylmethyl-*N*-methylcarbamoyloxy)ethyl]-3-[(*R*)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (13e)** Prepared from **12** (0.894 g, 2.19 mmol), the *p*-toluenesulfonic acid salt of benzyl *N*-methylglycinate[11] (1.54 g, 4.38 mmol), and triethylamine (0.61 ml, 4.38 mmol) as a pale yellow oil (0.884 g, 90%). IR (neat): 2950, 1750, 1710, 1450, 1380, 1150 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.22—1.79 (12H, m, $2\times CH_3$ and $(CH_2)_3$), 2.88—2.96 (1H, m, $C_3$-H), 2.97 (3H, s, NMe), 3.44—3.85 (3H, m, $C_4$-H and $OCH_2$), 3.92—4.24 (3H, m, $NCH_2COO$ and THP-OCH), 4.72—4.89 (2H, m, OCHO and CHOCO), 5.18 (2H, s, $PhCH_2$), 6.02 (1H, br s, NH), 7.36 (5H, s, $C_6H_5$). MS $m/z$: 449 $(M+1)^+$.

**(3*S*,4*S*)-4-[(*S*)-1-((4-Benzyloxycarbonylpiperazin-1-yl)carbonyloxy)ethyl]-3-[(*R*)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (13f)** 1-Benzyloxycarbonylpiperazine[12] (0.916 g, 4.16 mmol) was added to a solution of **12** (0.850 g, 2.08 mmol) in MeOH (5 ml) at 0 °C, and the mixture was stirred at the same temperature for 1 h. Concentration of the mixture *in vacuo* gave a residue which was purified by column chromatography ($SiO_2$, hexane–AcOEt (6:4)) to give **13f** as a colorless oil (0.929 g, 91%). IR (neat): 2950, 1760, 1690, 1430, 1230 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.22—1.80 (12H, m, $2\times CH_3$ and $(CH_2)_3$), 2.88—2.95 (1H, m, $C_3$-H), 3.47—3.65 (10H, m, $OCH_2$ and piperazine), 3.72 (1H, dd, $J$=2.2, 6.6 Hz, $C_4$-H), 3.98—4.23 (1H, m, THP-OCH), 4.72 (1H, br s, OCHO), 4.88 (1H, dq, $J$=each 6.6 Hz, CHOCO), 5.15 (2H, s, $PhCH_2$), 6.13 (1H, br s, NH), 7.35 (5H, s, $C_6H_5$). MS $m/z$: 489 $(M)^+$, 404 $(M-THP)^+$. The carbamates (**13g—i**) were prepared in a similar manner to that described above.

**(3*S*,4*S*)-4-[(*S*)-1-(*N*-(Pyridin-2-ylmethyl)carbamoyloxy)ethyl]-3-[(*R*)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (13g)** Prepared from **12** (0.822 g, 2.01 mmol) and 2-(aminomethyl)pyridine (0.414 ml, 4.02 mmol) as a pale yellow oil (0.728 g, 96%). IR (neat): 3300, 2950, 1750, 1710, 1250 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.22—1.86 (12H, m, $2\times CH_3$ and $(CH_2)_3$), 2.89—2.94 (1H, m, $C_3$-H), 3.55—4.23 (4H, m, $C_4$-H, $OCH_2$ and THP-OCH), 4.47 (2H, d, $J$=5.5 Hz, $NCH_2$), 4.73 (1H, br s, OCHO), 4.83 (1H, dq, $J$=each 6.6 Hz, CHOCO), 5.93 (1H, br s, NH), 6.44 (1H, br s, NH), 7.12—7.29 (2H, m, $C_3$-H and $C_5$-H of the pyridine ring), 7.67 (1H, ddd, $J$=1.8, 7.7, 7.7 Hz, $C_4$-H of the pyridine ring), 8.53 (1H, d, $J$=4.8 Hz, $C_6$-H of the pyridine ring). MS $m/z$: 276 $(M-THPO)^+$.

**(3*S*,4*S*)-4-[(*S*)-1-(*N*-Cyclopropylcarbamoyloxy)ethyl]-3-[(*R*)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (13h)** Prepared from **12** (0.520 g, 1.27 mmol) and cyclopropylamine (0.176 ml, 2.54 mmol) as a colorless oil (0.377 g, 91%). IR (neat): 3300, 2950, 1760, 1710, 1520, 1260, 1220 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.45—0.85 (4H, m, $CH_2CH_2$), 1.24—1.81 (12H, m, $2\times CH_3$ and $(CH_2)_3$), 2.49—2.64 (1H, m, NCH), 2.86—2.98 (1H, m, $C_3$-H), 3.49—4.11 (3H, m, THP-OCH and $OCH_2$), 3.69 (1H, dd, $J$=2.2, 6.6 Hz, $C_4$-H), 4.70—4.91 (3H, m, CHOCO, OCHO and NH), 6.02 (1H, br s, NH). MS $m/z$: 327 $(M+1)^+$, 225 $(M-THPO)^+$.

**(3*S*,4*S*)-4-[(*S*)-1-(*N*-(2-Hydroxyethyl)carbamoyloxy)ethyl]-3-[(*R*)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (13i)** Prepared from **12** (0.802 g, 1.96 mmol) and ethanolamine (0.237 ml, 3.92 mmol) as a colorless oil (0.600 g, 93%). IR (neat): 3300, 2950, 1760, 1710, 1520, 1260, 1220 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.22—1.80 (12H, m, $2\times CH_3$ and $(CH_2)_3$), 2.88—2.97 (1H, m, $C_3$-H), 3.32—3.44 (2H, m, $NCH_2CH_2$), 3.56—3.89 (5H, $C_4$-H, $OCH_2$ and $NCH_2CH_2O$), 4.00—4.24 (1H, m, THP-OCH), 4.68—5.01 (2H, m, OCHO and CHOCO), 5.20 (1H, br s, NH), 6.41 (1H, br s, NH). MS $m/z$: 245 $(M-THP)^+$, 229 $(M-THPO)^+$.

**(3*S*,4*S*)-4-[(*S*)-1-(*N*-Methoxycarbamoyloxy)ethyl]-3-[(*R*)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (13 l)** Prepared from **12** (0.490 g, 1.20 mmol), methoxylamine hydrochloride (0.301 g, 3.60 mmol), and triethylamine (0.5 ml, 3.60 mmol) as a colorless oil (0.323 g, 85%). IR (neat): 3300, 2950, 1750, 1440, 1380, 1250 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.23—1.82 (12H, m, $2\times CH_3$ and $(CH_2)_3$), 2.87—2.98 (1H, m, $C_3$-H), 3.34—3.87 (3H, m, $C_4$-H and $OCH_2$), 3.74 (3H, s, OMe), 4.00—4.24 (1H, m, THP-OCH), 4.72 (1H, br s, OCHO), 4.91 (1H, dq, $J$=6.4, 6.6 Hz, CHOCO), 6.06 (1H, br s, NH), 7.48 (1H, br s, NH). MS $m/z$: 215 $(M-THPO)^+$.

**(3*S*,4*S*)-4-[(*S*)-1-(*N*-Benzyl-*N*-benzyloxycarbamoyloxy)ethyl]-3-[(*R*)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (13n)** Trichloromethyl chloroformate[16] (80 $\mu$l, 0.67 mmol) was added to a mixture of **11** (0.326 g, 1.34 mmol) and pyridine (0.108 ml, 1.34 mmol) in $CH_2Cl_2$ (7.5 ml) at 0 °C under an argon atmosphere.[16] The mixture was stirred at the same temperature for 1.5 h. A solution of *N*-benzyl benzyloxyamine[13] (0.629 g, 2.95 mmol) in $CH_2Cl_2$ (2 ml) was added to the reaction mixture at 0 °C. After being stirred at the same temperature for 0.5 h, the mixture was diluted with $CH_2Cl_2$ (100 ml), washed successively with $H_2O$ and saturated NaCl, then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* followed by column chromatography ($SiO_2$, hexane–AcOEt (3:1)) of the residue gave **13n** as a colorless oil (0.440 g, 68%). IR (neat): 3300, 2960, 1760, 1710, 1450, 1380, 1240 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.25—1.82 (12H, m, $2\times CH_3$ and $(CH_2)_3$), 2.81—2.90 (1H, m, $C_3$-H), 3.49—4.23 (4H, m, THP-OCH, $C_4$-H and $OCH_2$), 4.59 (2H, s, $NCH_2Ph$), 4.62—5.03 (2H, m, CHOCO and OCHO), 4.74 (2H, s, $OCH_2Ph$), 5.56 (1H, br s, NH), 7.32 (10H, s, $2\times C_6H_5$). MS $m/z$: 482 $(M)^+$.

**(3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-carbamoyloxyethyl]-2-azetidinone (14a)** A mixture of **13a** (0.212 g, 0.74 mmol) and methanolic 1 N HCl (0.5 ml) in MeOH (10 ml) was stirred at room temperature for 0.5 h. Neutralization with triethylamine followed by concentration *in vacuo* gave a yellow oily residue. Benzyloxycarbonyl chloride (0.48 ml, 3.33 mmol) was added to a mixture of the residue and DMAP (0.451 g, 3.70 mmol) in $CH_2Cl_2$ (4.5 ml) at 0 °C. After being stirred at room temperature for 13 h, the mixture was diluted with $CH_2Cl_2$ (60 ml). The dichloromethane layer was separated, washed successively with $H_2O$, 0.5 N HCl, and saturated NaCl, then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue which was purified by column chromatography ($SiO_2$, hexane–AcOEt (3:7)) to give **14a** as a colorless needles (0.177 g, 71%). Recrystallization from AcOEt–$Et_2O$ gave an analytical sample of **14a** as colorless needles, mp 137—139 °C and $[\alpha]_D^{20}$ +11.6° ($c$=0.92, $CHCl_3$). IR (KBr): 3470, 3280, 1750, 1690, 1270 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.21 (3H, d, $J$=6.6 Hz, Me), 1.43 (3H, d, $J$=6.4 Hz, Me), 2.99—3.10 (1H, m, $C_3$-H), 3.63 (1H, dd, $J$=2.4, 6.8 Hz, $C_4$-H), 4.65—4.86 (3H, m, CHOCO and $NH_2$), 5.03—5.19 (3H, m, $PhCH_2$ and Z-OCH), 6.39 (1H, br s, NH), 7.35 (5H, s, $C_6H_5$). MS $m/z$: 336 $(M)^+$, 185 $(M-ZO)^+$. *Anal.* Calcd for $C_{16}H_{20}N_2O_6$: C, 57.13; H, 5.99; N, 8.33. Found: C, 56.89; H, 5.98; N, 8.20. The carbamates (**14b—h, l, n**) were prepared in the same manner as described above.

**(3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-methylcarbamoyloxy)ethyl]-2-azetidinone (14b)** Prepared from **13b** (0.318 g, 1.06 mmol) as a colorless oil (0.253 g, 68%). IR (neat): 3400, 1750, 1700, 1270 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.20 (3H, d, $J$=6.4 Hz, Me), 1.44 (3H, d, $J$=6.4 Hz, Me), 2.75 (3H, d, $J$=5.1 Hz, NMe), 2.99—3.11 (1H, m, $C_3$-H), 3.63 (1H, dd, $J$=2.4, 6.6 Hz, $C_4$-H), 4.67—4.89 (2H, m, CHOCO and NH), 5.03—5.19 (3H, m, $PhCH_2$ and Z-OCH), 6.09 (1H, br s, NH), 7.36 (5H, s, Ph). MS $m/z$: 350 $(M)^+$, 199 $(M-ZO)^+$.

**(3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-*N*,*N*-dimethylcarbamoyloxy)ethyl]-2-azetidinone (14c)** Prepared from **13c** (0.716 g, 2.27 mmol) as a colorless oil (0.479 g, 58%). IR (neat): 3250, 1750, 1680 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.22 (3H, d, $J$=6.4 Hz, Me), 1.44 (3H, d, $J$=6.4 Hz, Me), 2.88 (6H, s, $Me_2N$), 2.99—3.11 (1H, m, $C_3$-H), 3.67 (1H, dd, $J$=2.4, 6.6 Hz, $C_4$-H), 4.82 (1H, dq, $J$=6.4, 6.6 Hz, CHOCO),

5.05—5.27 (3H, m, $PhCH_2$ and Z-OCH), 6.00 (1H, br s, NH), 7.36 (5H, s, Ph). MS *m/z*: 365 $(M)^+$. 213 $(M-151)^+$.

**(3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-benzyloxycarbonylmethyl)carbamoyloxy)ethyl]-2-azetidinone (14d)** Prepared from **13d** (0.691 g, 1.54 mmol) as a colorless oil (0.671 g, 90%). IR (neat): 3350, 1750, 1720, 1260 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.20 (3H, d, $J$=6.4 Hz, Me), 1.44 (3H, d, $J$=6.4 Hz, Me), 2.95—3.11 (1H, m, $C_3$-H), 3.63 (1H, dd, $J$=2.2, 6.8 Hz, $C_4$-H), 3.95 (2H, d, $J$=5.7 Hz, $NCH_2COO$), 4.83 (1H, dq, $J$=6.4, 6.8 Hz, CHOCO), 5.01—5.29 (6H, m, NH, Z-OCH and 2×$PhCH_2$), 6.11 (1H, br s, NH), 7.35 (10H, s, 2×Ph). MS *m/z*: 407 $(M-Ph)^+$, 333 $(M-ZO)^+$.

**(3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-benzyloxycarbonylmethyl-*N*-methylcarbamoyloxy)ethyl]-2-azetidinone (14e)** Prepared from **13e** (0.691 g, 1.54 mmol) as a colorless oil (0.544 g, 70%). IR (neat): 1750, 1700, 1450, 1380, 1260 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.11 (3H, d, $J$=6.4 Hz, Me), 1.43 (3H, d, $J$=6.4 Hz, Me), 2.95 (3H, s, NMe), 2.91—3.08 (1H, m, $C_3$-H), 3.60—3.72 (1H, m, $C_4$-H), 4.05 (2H, s, $NCH_2COO$), 4.74—4.89 (1H, m, CHOCO), 5.03—5.22 (5H, m, 2×$PhCH_2$ and Z-OCH), 6.03 (1H, br s, NH), 7.35 (10H, s, 2×Ph). MS *m/z*: 498 $(M)^+$, 347 $(M-ZO)^+$.

**(3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-((4-benzyloxycarbonylpiperazin-1-yl)carbonyloxy)ethyl]-2-azetidinone (14f)** Prepared from **13f** (0.885 g, 1.81 mmol) as a colorless oil (0.751 g, 77%). IR (neat): 3300, 1770, 1700, 1460, 1430, 1260 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.22 (3H, d, $J$=6.2 Hz, Me), 1.44 (3H, d, $J$=6.4 Hz, Me), 2.97—3.10 (1H, m, $C_3$-H), 3.44 (8H, s, piperazine), 3.67 (1H, dd, $J$=2.4, 6.6 Hz, $C_4$-H), 4.85 (1H, dq, $J$=6.4, 6.6 Hz, CHOCO), 5.03—5.34 (5H, m, 2×$PhCH_2$ and ZOCH), 6.08 (1H, br s, NH), 7.35 (10H, s, 2×$C_6H_5$). MS *m/z*: 539 $(M)^+$, 388 $(M-Z)^+$.

**(3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-pyridin-2-ylmethyl)carbamoyloxy)ethyl]-2-azetidinone (14g)** Prepared from **13g** (0.726 g, 1.92 mmol) as a pale yellow oil (0.591 g, 72%). IR (neat): 3300, 2930, 1760, 1520, 1385, 1260 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.22 (3H, d, $J$=6.4 Hz, Me), 1.44 (3H, d, $J$=6.4 Hz, Me), 2.98—3.08 (1H, m, $C_3$-H), 3.63 (1H, dd, $J$=2.2, 7.3 Hz, $C_4$-H), 4.45 (2H, d, $J$=5.5 Hz, $NCH_2COO$), 4.84 (1H, dq, $J$=6.4, 7.3 Hz, CHOCO), 4.96—5.26 (3H, m, $PhCH_2$ and Z-OCH), 5.87 (1H, br s, NH), 6.45 (1H, br s, NH), 7.12—7.26 (2H, m, $C_3$-H and $C_5$-H of the pyridine ring), 7.35 (5H, s, $C_6H_5$), 7.57—7.76 (1H, m, $C_4$-H of the pyridine ring), 8.53 (1H, d, $J$=4.8 Hz, $C_6$-H of the pyridine ring). MS *m/z*: 427 $(M)^+$, 276 $(M-ZO)^+$.

**(3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-cyclopropylcarbamoyloxy)ethyl]-2-azetidinone (14h)** Prepared from **13h** (0.336 1.03 mmol) as a colorless oil (0.314 g, 81%). IR (neat): 3300, 3030, 1760, 1510, 1390, 1260 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.44—0.83 (4H, m, $CH_2CH_2$), 1.21 (3H, d, $J$=6.4 Hz, Me), 1.44 (3H, d, $J$=6.4 Hz, Me), 2.47—2.67 (1H, m, NCH), 2.98—3.11 (1H, m, $C_3$-H), 3.64 (1H, dd, $J$=2.5, 6.6 Hz, $C_4$-H), 4.66—5.19 (5H, m, CHOCO, Z-OCH, $PhCH_2$ and NH), 6.02 (1H, br s, NH), 7.36 (5H, s, $C_6H_5$). MS *m/z*: 376 $(M)^+$, 225 $(M-ZO)^+$.

**(3*S*,4*S*)-4-[(*S*)-1-(*N*-(2-Benzyloxycarbonyloxyethyl)carbamoyloxy)-ethyl]-3-[(*R*)-1-(benzyloxycarbonyloxy)ethyl]-2-azetidinone (14i)** Treatments of **13i** (0.615 g, 1.86 mmol) in a similar manner to that described for the preparation of **14a** effected simultaneous benzyloxycarbonylation of the primary and secondary alcohols, giving **14i** as a colorless oil (0.699 g, 73%). IR (neat): 3330, 2970, 1750, 1690, 1520, 1380, 1250 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.19 (3H, d, $J$=6.6 Hz, Me), 1.44 (3H, d, $J$=6.4 Hz, Me), 2.95—3.08 (1H, m, $C_3$-H), 3.33—3.51 (2H, m, $NCH_2CH_2O$), 3.59 (1H, dd, $J$=2.2, 7.0 Hz, $C_4$-H), 4.16—4.29 (2H, m, $NCH_2CH_2O$), 4.73—5.29 (6H, m, CHOCO, Z-OCH and 2×$PhCH_2$), 6.05 (1H, br s, NH), 7.35 (5H, s, $C_6H_5$), 7.37 (5H, s, Ph). MS *m/z*: 514 $(M)^+$.

**(3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-phenylcarbamoyloxy)ethyl]-2-azetidinone (14j)** A mixture of **12** (0.539 g, 1.32 mmol) and aniline (5 ml) was stirred at 60 °C for 10 h, and then diluted with AcOEt (150 ml). The ethyl acetate solution was washed successively with 1 N HCl, $H_2O$, and saturated NaCl, then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave crude **13j** as a dark red oil which was dissolved in MeOH (12 ml). Methanolic 1 N HCl (2 ml) was added to the methanolic solution. After being stirred at room temperature for 1 h, the mixture was neutralized with triethylamine and diluted with AcOEt (70 ml). The ethyl acetate solution was washed successively with $H_2O$ and saturated NaCl, then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* followed by column chromatography ($SiO_2$, hexane–AcOEt (1 : 10)) of the residue gave a colorless oil. Benzyloxycarbonyl chloride (0.942 ml, 6.60 mmol) was added to a mixture of the colorless oil and DMAP (0.855 g, 7.26 mmol) in $CH_2Cl_2$ (11 ml) at 0 °C. After being stirred at room temperature for 16 h, the mixture was diluted with $CH_2Cl_2$ (60 ml). The organic layer was separated, washed successively with $H_2O$ and saturated NaCl, then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue which was purified by column chromatography ($SiO_2$, hexane–AcOEt (6 : 4)) to give **14j** as a colorless oil (0.289 g, 53%). IR (neat): 3310, 2980, 1750, 1590, 1530, 1440, 1250 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.27 (3H, d, $J$=6.4 Hz, Me), 1.44 (3H, d, $J$=6.4 Hz, Me), 3.03—3.14 (1H, m, $C_3$-H), 3.70 (1H, dd, $J$=2.4, 6.6 Hz, $C_4$-H), 4.84—5.27 (4H, m, CHOCO, Z-OCH and $PhCH_2$), 6.23 (1H, br s, NH), 6.76 (1H, br s, NH), 7.23—7.35 (10H, m, 2×$C_6H_5$). MS *m/z*: 412 $(M)^+$.

**(3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-(4-fluorophenyl)carbamoyloxy)ethyl]-2-azetidinone (14k)** Prepared from **12** (0.749 g, 1.83 mmol) in a similar manner to that described for the preparation of **14j**. The compound (**14k**) was obtained as a colorless oil (0.482 g, 61%). IR (neat): 3330, 3000, 1760, 1670, 1540, 1510, 1390, 1260 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.27 (3H, d, $J$=6.4 Hz, Me), 1.44 (3H, d, $J$=6.2 Hz, Me), 3.02—3.15 (1H, m, $C_3$-H), 3.70 (1H, dd, $J$=2.4, 6.6 Hz, $C_4$-H), 4.84—5.20 (4H, m, CHOCO, Z-OCH and $PhCH_2$), 6.22 (1H, br s, NH), 6.74 (1H, br s, NH), 6.88—7.39 (4H, m, $C_6H_4F$), 7.35 (5H, s, $C_6H_5$). MS *m/z*: 430 $(M)^+$.

**(3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-methoxycarbamoyloxy)ethyl]-2-azetidinone (14l)** Prepared from **13l** (0.289, 0.91 mmol) as a colorless oil (0.197 g, 59%). IR (neat): 3320, 1760, 1385, 1270 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.32 (3H, d, $J$=6.4 Hz, Me), 1.41 (3H, d, $J$=6.6 Hz, Me), 2.88—3.00 (1H, m, $C_3$-H), 3.73 (1H, dd, $J$=2.2, 5.9 Hz, $C_4$-H), 3.80 (3H, s, OMe), 4.18 (1H, dq, $J$=6.4, 5.9 Hz, CHOCO), 4.94 (1H, dq, $J$=each 6.6 Hz, Z-OCH), 5.29 (2H, s, $PhCH_2$), 6.13 (1H, br s, NH), 7.39 (6H, s, $C_6H_5$ and NH). MS *m/z*: 366 $(M)^+$.

**(3*S*,4*S*)-4-[(*S*)-1-(*N*-Benzyl-*N*-methoxycarbamoyloxyethyl]-3-[(*R*)-1-(benzyloxycarbonyloxy)ethyl]-2-azetidinone (14m)** Trichloromethyl chloroformate (0.11 ml, 0.92 mmol) was added to a mixture of **11** (0.445 g, 1.83 mmol) and pyridine (0.148 ml, 1.83 mmol) in $CH_2Cl_2$ (10 ml) at 0 °C under an argon atmosphere, and the mixture was stirred at the same temperature for 2.5 h. A solution of *N*-benzylmethoxyamine[15] (0.552 g, 4.03 mmol) in $CH_2Cl_2$ (3 ml) was added to the reaction mixture. The mixture was stirred at 0 °C for 0.5 h, then diluted with $CH_2Cl_2$ (100 ml). The dichloromethane solution was washed successively with $H_2O$ and saturated NaCl, then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* followed by column chromatography ($SiO_2$, hexane–AcOEt (3 : 2)) of the residue gave **13m** as a colorless oil. A mixture of **13m** and methanolic 1 N HCl (2.5 ml) in MeOH (15 ml) was stirred at room temperature for 1 h. The mixture was neutralized with triethylamine and diluted with AcOEt (100 ml). The ethyl acetate solution was washed successively with $H_2O$ and saturated NaCl, then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave a colorless oil. Benzyloxycarbonyl chloride (1.09 ml, 0.77 mmol) was added to a mixture of the colorless oil and DMAP (1.03 g, 8.42 mmol) in $CH_2Cl_2$ (11 ml) at 0 °C. After being stirred at room temperature for 18 h, the mixture was diluted with $CH_2Cl_2$ (80 ml). The dichloromethane solution was washed successively with $H_2O$ and saturated NaCl, then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* followed by purification by column chromatography ($SiO_2$, hexane–AcOEt (3 : 1)) gave **14m** as a colorless oil (0.376 g, 45%). IR (neat): 3300, 3000, 1765, 1740, 1710, 1450, 1380, 1260 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.23 (3H, d, $J$=6.4 Hz, Me), 1.41 (3H, d, $J$=6.4 Hz, Me), 2.90—3.03 (1H, m, $C_3$-H), 3.54—3.67 (1H, m, $C_4$-H), 3.60 (3H, s, OMe), 4.61 (2H, s, $NCH_2Ph$), 4.74—5.23 (4H, m, CHOCO, Z-OCH and $PhCH_2$), 5.82 (1H, br s, NH), 7.31 (5H, s, $C_6H_5$), 7.35 (5H, s, $C_6H_5$). MS *m/z*: 305 $(M-ZO)^+$.

**(3*S*,4*S*)-4-[(*S*)-1-(*N*-Benzyl-*N*-benzyloxycarbamoyloxy)ethyl]-3-[(*R*)-1-(benzyloxycarbonyloxy)ethyl]-2-azetidinone (14n)** Prepared from **13n** (0.395 g, 0.82 mmol) as a colorless oil (0.310 g, 71%). IR (neat): 3300, 3050, 1770, 1750, 1710, 1450, 1380, 1260 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.20 (3H, d, $J$=6.4 Hz, Me), 1.41 (3H, d, $J$=6.4 Hz, Me), 2.88—3.01 (1H, m, $C_3$-H), 3.55 (1H, dd, $J$=2.4, 7.5 Hz, $C_4$-H), 4.56 (2H, s, $NCH_2Ph$), 4.73 (2H, s, $OCH_2Ph$), 4.69—5.19 (4H, m, CHOCO, Z-OCH and $PhCH_2$), 5.54 (1H, br s, NH), 7.32 (10H, s, 2×$C_6H_5$), 7.35 (5H, s, $C_6H_5$). MS *m/z*: 532 $(M)^+$, 381 $(M-ZO)^+$.

**Tetrabutylammonium (3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbamoyloxy)ethyl]-4-[(*S*)-1-carbamoyloxyethyl]-2-azetidinone-1-sulfonate (15a)** A mixture of **14a** (0.107 g, 0.32 mmol) and $SO_3$–Py (0.204 g, 1.28 mmol) in *N*,*N*-dimethylformamide (DMF) (0.5 ml) was stirred at 50 °C for 6 h. Tetrabutylammonium hydrogensulfate (0.109 g, 0.32 mmol) and 0.5 M $KH_2PO_4$ (15 ml) were added, and the mixture was extracted with $CH_2Cl_2$. The dichloromethane extracts were combined and dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue, which

was purified by column chromatography ($SiO_2$, AcOEt–MeOH (10 : 1)) to give **15a** as a pale yellow oil (0.171 g, 81%). IR (neat): 3500, 3350, 2930, 1750, 1695, 1450, 1380 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.98 (12H, t, 4 × $(CH_2)_3CH_3$), 1.25—1.71 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$), 3.05 (1H, dd, $J$=2.6, 6.4 Hz, $C_3$-H), 3.15—3.33 (8H, m, 4 × $CH_2CH_2CH_2CH_3$), 4.04 (1H, dd, $J$=2.6, 4.4 Hz, $C_4$-H), 4.64 (2H, br s, $NH_2$), 4.93—5.29 (4H, m, CHOCO, Z-OCH and $PhCH_2$), 7.35 (5H, s, $C_6H_5$). The ammonium salts (**15b—k, m, n**) were prepared in the same manner as described above.

**Tetrabutylammonium (3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-methylcarbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (15b)** Prepared from **14b** (0.187 g, 0.53 mmol) as a pale yellow oil (0.320 g, 88%). IR (neat): 2970, 1760, 1710, 1260, 1040 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.99 (12H, t, 4 × $(CH_2)_3CH_3$), 1.24—1.74 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$), 2.56 (3H, d, $J$=4.8 Hz, NMe), 3.05 (1H, dd, $J$=2.4, 6.6 Hz, $C_3$-H), 3.14—3.34 (8H, m, 4 × $CH_2CH_2CH_2CH_3$), 4.03 (1H, dd, $J$=2.4, 4.6 Hz, $C_4$-H), 4.71 (1H, br s, NH), 4.97—5.29 (4H, m, CHOCO, Z-OCH and $PhCH_2$), 7.35 (5H, s, $C_6H_5$).

**Tetrabutylammonium (3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*,*N*-dimethylcarbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (15c)** Prepared from **14c** (99 mg, 0.27 mmol) as a colorless oil (0.172 g, 93%). IR (neat): 3500, 2950, 1750, 1690, 1380, 1250 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.99 (12H, t, 4 × $(CH_2)_3CH_3$), 1.25—1.74 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$), 2.80 (6H, s, $N(CH_3)_2$), 3.08 (1H, dd, $J$=2.4, 6.4 Hz, $C_3$-H), 3.14—3.35 (8H, m, 4 × $CH_2CH_2CH_2CH_3$), 4.05 (1H, dd, $J$=2.4, 4.4 Hz, $C_4$-H), 4.95—5.35 (4H, m, CHOCO, Z-OCH and $PhCH_2$), 7.34 (5H, s, $C_6H_5$).

**Tetrabutylammonium (3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-(benzyloxycarbonylmethyl)carbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (15d)** Prepared from **14d** (0.190 g, 0.39 mmol) as a colorless oil (0.255 g, 81%). IR (neat): 3370, 2970, 1760, 1680, 1260, 1220 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.00 (12H, t, 4 × $(CH_2)_3CH_3$), 1.26—1.72 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$), 3.07—3.35 (9H, m, $C_3$H and 4 × $CH_2CH_2CH_2CH_3$), 3.78 (2H, d, $J$=5.7 Hz, $NCH_2COO$), 4.06 (1H, dd, $J$=2.4, 4.8 Hz, $C_4$-H), 4.96—5.38 (7H, m, CHOCO, Z-OCH, 2 × $PhCH_2$ and NH), 7.34 (10H, s, 2 × $C_6H_5$).

**Tetrabutylammonium (3*S*,4*S*)-4-[(*S*)-1-(*N*-Benzyloxycarbonylmethyl-*N*-methylcarbamoyloxy)ethyl]-3-[(*R*)-1-(benzyloxycarbonyloxy)ethyl]-2-azetidinone-1-sulfonate (15e)** Prepared from **14e** (0.274 g, 0.55 mmol) as a colorless oil (0.415 g, 92%). IR (neat): 2970, 1750, 1700, 1450, 1260 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.99 (12H, t, 4 × $(CH_2)_3CH_3$), 1.25—1.74 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$), 2.88 (3H, S, NMe), 3.05 (1H, dd, $J$=2.2, 6.6 Hz, $C_3$-H), 3.11—3.33 (8H, m, 4 × $CH_2CH_2CH_2CH_3$), 3.96—4.32 (3H, m, $C_4$-H and $NCH_2COO$), 4.98—5.37 (6H, m, CHOCO, Z-OCH and 2 × $PhCH_2$), 7.33 (10H, s, 2 × $C_6H_5$).

**Tetrabutylammonium (3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-((4-benzyloxycarbonylpiperazin-1-yl)carbonyloxy)ethyl]-2-azetidinone-1-sulfonate (15f)** Prepared from **14f** (0.479 g, 0.89 mmol) as a colorless oil (0.736 g, 96%). IR (neat): 2970, 1760, 1690, 1420, 1250 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.99 (12H, t, 4 × $(CH_2)_3CH_3$), 1.23—1.73 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$), 3.08 (1H, dd, $J$=2.2, 6.8 Hz, $C_3$-H), 3.16—3.51 (16H, m, piperazine and 4 × $CH_2CH_2CH_2CH_3$), 4.02 (1H, dd, $J$=2.2, 5.7 Hz, $C_4$-H), 4.94—5.29 (6H, m, CHOCO, Z-OCH and 2 × $PhCH_2$), 7.32 (5H, s, $C_6H_5$), 7.33 (5H, s, $C_6H_5$).

**Tetrabutylammonium (3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-(pyridin-2-ylmethyl)carbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (15g)** Prepared from **14g** (0.413 g, 0.97 mmol) as a colorless oil (0.646 g, 89%). IR (neat): 3030, 2990, 1760, 1720, 1510, 1270 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.99 (12H, t, 4 × $(CH_2)_3CH_3$), 1.23—1.73 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$), 3.08 (1H, dd, $J$=2.6, 6.4 Hz, $C_3$-H), 3.16—3.35 (8H, m, 4 × $CH_2CH_2CH_2CH_3$), 4.10 (1H, dd, $J$=2.6, 4.8 Hz, $C_4$-H), 4.38 (2H, d, $NCH_2$), 4.98—5.29 (4H, m, CHOCO, Z-OCH and $PhCH_2$), 5.68 (1H, br s, NH), 7.10—7.20 (2H, m, $C_3$-H and $C_5$-H of the pyridine ring), 7.29 (5H, s, $C_6H_5$), 7.62 (1H, ddd, $J$=2.0, 7.7, 8.0 Hz, $C_4$-H of the pyridine ring). 8.48 (1H, d, $J$=4.6 Hz, $C_6$-H of the pyridine ring).

**Tetrabutylammonium (3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-cyclopropylcarbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (15h)** Prepared from **14h** (0.232 g, 0.62 mmol) as a colorless oil (0.388 g, 90%). IR (neat): 3350, 2970, 2900, 1760, 1710, 1670, 1500, 1450, 1250 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.41—0.75 (4H, m, $CH_2CH_2$), 1.00 (12H, t, 4 × $(CH_2)_3CH_3$), 1.26—1.74 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$), 2.44—2.57 (1H, m, NCH), 3.05 (1H, dd, $J$=2.6, 9.0 Hz, $C_3$-H), 3.14—3.34 (8H, m, 4 × $CH_2CH_2CH_2CH_3$), 4.04 (1H, dd, $J$=2.6, 5.1 Hz, $C_4$-H), 4.92—5.29 (5H, m, CHOCO, Z-OCH, $PhCH_2$ and NH), 7.35 (5H, s, $C_6H_5$).

**Tetrabutylammonium (3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-(2-(benzyloxycarbonyloxy)ethyl)carbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (15i)** Prepared from **14i** (0.615 g, 1.86 mmol) as a colorless oil (0.699 g, 73%). IR (neat): 3350, 2980, 2880, 1760, 1670, 1530, 1450, 1380 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.99 (12H, t, 4 × $(CH_2)_3CH_3$), 1.25—1.79 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$), 2.99—3.46 (11H, m, $C_3$-H, 4 × $CH_2CH_2CH_2CH_3$ and $NCH_2CH_2O$), 4.00—4.16 (3H, m, $C_4$-H and $NCH_2CH_2O$), 4.95—5.45 (6H, m, CHOCO, Z-OCH and 2 × $PhCH_2$), 7.32 (5H, s, $C_6H_5$), 7.35 (5H, s, $C_6H_5$).

**Tetrabutylammonium (3*S*,4*S*)-3-[(*R*)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-phenylcarbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (15j)** Prepared from **14j** (0.249 g, 0.60 mmol) as a colorless oil (0.426 g, 97%). IR (neat): 3280, 2970, 1760, 1670, 1600, 1550, 1250 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.99 (12H, t, 4 × $(CH_2)_3CH_3$), 1.23—1.74 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$), 3.07 (1H, dd, $J$=2.6, 6.8 Hz, $C_3$-H), 3.15—3.32 (8H, m, 4 × $CH_2CH_2CH_2CH_3$), 4.09 (1H, dd, $J$=2.6, 5.5 Hz, $C_4$-H), 4.91—5.29 (4H, m, CHOCO, Z-OCH and $PhCH_2$), 7.29 (10H, s, 2 × $C_6H_5$).

**Tetrabutylammonium (3*S*,4*S*)-3-[(*R*)-1-Benzyloxycarbonyloxy)ethyl]-4-[(*S*)-1-(*N*-(4-fluorophenyl)carbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (15k)** Prepared from **14k** (0.391 g, 0.91 mmol) as a colorless oil (0.657 g, 96%). IR (neat): 3300, 2980, 1760, 1670, 1510, 1250 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.98 (12H, t, 4 × $(CH_2)_3CH_3$), 1.25—1.72 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$) 3.04 (1H, dd, $J$=2.4, 6.2 Hz, $C_3$-H), 3.14—3.32 (8H, m, 4 × $CH_2CH_2CH_2CH_3$), 4.08 (1H, dd, $J$=2.4, 5.5 Hz, $C_4$-H), 4.94—5.26 (4H, m, CHOCO, Z-OCH and $PhCH_2$), 6.79—7.34 (4H, m, $C_6H_4F$), 7.30 (5H, s, $C_6H_5$).

**Tetrabutylammonium (3*S*,4*S*)-4-[(*S*)-1-(*N*-Benzyl-*N*-methoxycarbamoyloxy)ethyl]-3-[(*R*)-1-(benzyloxycarbonyloxy)ethyl]-2-azetidinone-1-sulfonate (15m)** Prepared from **14m** (0.137 g, 0.30 mmol) as a colorless oil (0.215 g, 92%). IR (neat): 2980, 1770, 1710, 1455, 1370, 1260 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.99 (12H, t, 4 × $(CH_2)_3CH_3$), 1.26—1.74 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$), 3.06—3.36 (9H, m, $C_3$-H and 4 × $CH_2CH_2CH_2CH_3$), 3.52 (3H, s, OMe), 4.14 (1H, dd, $J$=2.6, 5.9 Hz, $C_4$-H), 4.49 (1H, d, $J$=15.6 Hz, NCHPh), 4.73 (1H, d, $J$=15.6 Hz, NCHPh), 4.98—5.43 (4H, m, CHOCO, Z-OCH and $PhCH_2$), 7.27 (5H, s, $C_6H_5$), 7.32 (5H, s, $C_6H_5$).

**Tetrabutylammonium (3*S*,4*S*)-4-[(*S*)-1-(*N*-Benzyl-*N*-benzyloxycarbamoyloxy)ethyl]-3-[(*R*)-1-(benzyloxycarbonyloxy)ethyl]-2-azetidinone-1-sulfonate (15n)** Prepared from **14n** (0.229 g, 0.43 mmol) as a colorless oil (0.329 g, 90%). IR (neat): 2960, 2900, 1770, 1700, 1450, 1380, 1260 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.98 (12H, t, 4 × $(CH_2)_3CH_3$), 1.25—1.72 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$), 3.06 (1H, dd, $J$=2.4, 5.9 Hz, $C_3$-H), 3.15—3.33 (8H, m, 4 × $CH_2CH_2CH_2CH_3$), 4.15 (1H, dd, $J$=2.4, 4.6 Hz, $C_4$-H), 4.51—5.26 (8H, m, CHOCO, Z-OCH and 3 × $PhCH_2$). 7.30 (15H, s, 3 × $C_6H_5$).

**(3*S*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-4-[(*S*)-1-(*N*-((1-methylpyridinium-2-yl)-methyl)carbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (16)** A mixture of **15g** (0.111 g, 0.15 mmol) and 5% Pd–C (40 mg) in THF (4 ml) was stirred at room temperature under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give the corresponding secondary alcohol as a colorless oil (73.4 mg, 80%). $^1$H-NMR ($CDCl_3$) $\delta$: 0.99 (12H, t, 4 × $(CH_2)_3CH_3$), 1.26—1.78 (22H, m, 2 × Me and 4 × $CH_2CH_2CH_2CH_3$), 2.90—2.97 (1H, m, $C_3$-H), 3.17—3.34 (8H, m, 4 × $CH_2CH_2CH_2CH_3$), 4.06—4.19 (2H, m, $C_4$-H and HO-CH), 4.45 (2H, d, $J$=5.7 Hz, $NCH_2$), 5.26—5.39 (1H, m, CHOCO), 5.89 (1H, br s, NH), 7.09—7.35 (2H, m, $C_2$-H and $C_5$-H of the pyridine ring), 7.57—7.74 (1H, m, $C_4$-H of the pyridine ring), 8.48 (1H, d, $J$=5.1 Hz, $C_6$-H of the pyridine ring). A mixture of the secondary alcohol (73.4 mg, 0.12 mmol) and MeI (4 ml) in acetone (4 ml) was stirred at room temperature for 1.5 h under shielding from light. The precipitate was filtered off and washed with acetone to give **16** as a white powder (43.1 mg, 93%), $[\alpha]_D^{20}$ −7.2° ($c$=1.03, $H_2O$). IR (KBr): 3430, 2970, 1750, 1710, 1630, 1510, 1250 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 1.28 (3H, d, $J$=6.0 Hz, Me), 1.35 (3H, d, $J$=6.5 Hz, Me), 2.86 (1H, d, $J$=5.5 Hz, $C_3$-H), 4.01—4.07 (2H, m, $C_4$-H and HO-CH), 4.35 (3H, s, NMe), 4.62 (1H, d, $J$=17.1 Hz, NCH), 4.80 (1H, d, $J$=17.1 Hz, NCH), 4.97—5.01 (1H, m, CHOCO), 7.91 (1H, dd, $J$=5.9, 7.9 Hz, $C_5$-H of the pyridine ring), 8.26 (1H, d, $J$=7.9 Hz, $C_3$-H of the pyridine ring), 8.50 (1H, t, $J$=7.9 Hz, $C_4$-H of the pyridine ring), 8.84 (1H, d, $J$=5.9 Hz, $C_6$-H of the pyridine ring). MS (SIMS) $m/z$: 388 $(M+H)^+$, 386 $(M-H)^-$, 372 $(M-Me)^-$. *Anal.* Calcd for $C_{15}H_{21}N_3O_7S \cdot H_2O$: C, 44.43; H, 5.72; N, 10.36. Found: C, 44.49; H, 5.34; N, 10.14.

**Potassium (3*S*,4*S*)-4-[(*S*)-1-Carbamoyloxyethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone-1-sulfonate (9a)** A mixture of **15a** (0.160 g, 0.24 mmol) and 5% Pd–C (16 mg) in THF (5 ml) was stirred at room temperature for 3 h under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give a colorless oil.

This was dissolved in a small amount of acetone–$H_2O$ and chromatographed on an anion exchange resin[AG 50W-X2($K^+$ form)]. Elution of the column with $H_2O$ and lyophilization of the combined eluate gave **9a** as a white powder (70 mg, 91%). $[\alpha]_D^{20}$ −32.2° ($c$=1.01, $H_2O$). IR (KBr): 3450, 1760, 1690, 1250 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 1.27 (3H, d, $J$=6.6 Hz, Me), 1.36 (3H, d, $J$=6.6 Hz, Me), 2.97 (1H, dd, $J$=2.6, 6.2 Hz, $C_3$-H), 4.01—4.18 (1H, m, HO-CH), 4.14 (1H, dd, $J$=2.6, 4.4 Hz, $C_4$-H), 5.09—5.24 (1H, m, CHOCO). MS (SIMS) $m/z$: 281 $(M-K)^-$. *Anal.* Calcd for $C_8H_{13}KN_2O_7S\cdot1.5H_2O$: C, 27.66; H, 4.64; N, 8.07. Found: C, 28.13; H, 4.58; N, 7.69. The potassium salts (**9b—k,m,n**) were prepared from the ammonium salts (**15b—k,m,n**) in the same manner as described above.

**Potassium (3*S*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-4-[(*S*)-1-(*N*-methylcarbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (9b)** Prepared from **15b** (0.305 g, 0.44 mmol) as a white powder (0.131 g, 89%), $[\alpha]_D^{20}$ −20.6° ($c$=1.49, $H_2O$). IR (KBr): 3430, 3000, 1760, 1710, 1530, 1260, 1040 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 1.26 (3H, d, $J$=6.6 Hz, Me), 1.34 (3H, d, $J$=6.6 Hz, Me), 2.70 (3H, s, NMe), 2.99 (1H, dd, $J$=2.6, 5.9 Hz, $C_3$-H), 4.01—4.19 (2H, m, $C_4$-H and HO-CH), 5.05—5.32 (1H, m, CHOCO). MS (SIMS) $m/z$: 335 $(M+H)^+$, 373 $(M+K)^+$. *Anal.* Calcd for $C_9H_{15}KN_2O_7S\cdot H_2O$: C, 30.67; H, 4.86; N, 7.95. Found: C, 30.90; H, 4.83; N, 7.93.

**Potassium (3*S*,4*S*)-4-[(*S*)-1-(*N*,*N*-Dimethylcarbamoyloxy)ethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone-1-sulfonate (9c)** Prepared from **15c** (21 mg, 0.03 mmol) as a white powder (9.3 mg, 89%), $[\alpha]_D^{20}$ −9.8° ($c$=1.51, $H_2O$). IR (KBr): 3460, 2970, 1750, 1680, 1390, 1250 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 1.27 (3H, d, $J$=6.4 Hz, Me), 1.36 (3H, d, $J$=6.6 Hz, Me), 2.91 (6H, s, $Me_2N$), 2.99 (1H, dd, $J$=2.6, 6.2 Hz, $C_3$-H), 4.01—4.17 (2H, m, $C_4$-H and HO-CH), 5.12—5.25 (1H, m, CHOCO). MS (SIMS) $m/z$: 309 $(M-K)^-$. *Anal.* Calcd for $C_{10}H_{17}KN_2O_7S\cdot1.5H_2O$: C, 31.99; H, 5.37; N, 7.46. Found: C, 32.02; H, 5.43; N, 7.72.

**Dipotassium (3*S*,4*S*)-4-[(*S*)-1-(*N*-Carboxylatomethylcarbamoyloxy)ethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone-1-sulfonate (9d)** Prepared from **15d** (0.212 g, 0.26 mmol) as a white powder (79.6 mg, 74%), $[\alpha]_D^{20}$ −31.0° ($c$=1.21, $H_2O$). IR (KBr): 3370, 1760, 1690, 1610, 1540, 1250, 1150 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.10 (3H, d, $J$=5.9 Hz, Me), 1.17 (3H, d, $J$=6.4 Hz, Me), 2.78 (1H, dd, $J$=2.4, 5.9 Hz, $C_3$-H), 3.25 (2H, d, $J$=4.6 Hz, $NCH_2COO$), 3.66—3.92 (2H, m, $C_4$-H and HO-CH), 5.04—5.20 (1H, m, CHOCO), 5.98 (1H, brs, NH). MS (SIMS) $m/z$: 417 $(M+H)^+$, 455 $(M+K)^+$. *Anal.* Calcd for $C_{10}H_{14}K_2N_2O_9S\cdot1.3H_2O$: C, 27.30; H, 3.80; N, 6.37. Found: C, 27.59; H, 4.12; N, 6.50.

**Dipotassium (3*S*,4*S*)-4-[(*S*)-1-(*N*-Carboxylatomethyl-*N*-methylcarbamoyloxy)ethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone-1-suflonate (9e)**[13] Prepared from **15e** (0.415 g, 0.51 mmol) as a white powder (0.178 g, 83%). $[\alpha]_D^{20}$ −15.7° ($c$=1.67, $H_2O$). IR (KBr): 3500, 3000, 1760, 1690, 1600, 1410, 1240 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.10 (1.5H, d, $J$=6.5 Hz, Me), 1.12 (1.5H, d, $J$=6.5 Hz, Me), 1.14 (1.5 H, d, $J$=6.5 Hz, Me), 1.21 (1.5H, d, $J$=6.5 Hz, Me), 2.75 (0.5H, dd, $J$=2.2, 6.5 Hz, $C_3$-H), 2.79 (1.5H, s, NMe), 2.82 (2H, brs, $C_3$-H and NMe), 3.69 (2H, brs, $NCH_2COO$), 3.71—3.78 (0.5H, m, HO-CH), 3.82—3.88 (0.5H, m, HO-CH), 3.87 (0.5H, dd, $J$=2.2, 4.3 Hz, $C_4$-H), 3.91 (0.5H, dd, $J$=2.2, 4.3 Hz, $C_4$-H), 5.06 (0.5H, dq, $J$=4.3, 6.4 Hz, CHOCO), 5.13 (0.5H, dq, $J$=4.3, 6.4 Hz, CHOCO).[13] MS (SIMS) $m/z$: 431 $(M+H)^+$, 469 $(M+K)^+$.

**Potassium (3*S*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-4-[(*S*)-1-((piperazin-1-yl)carbonyloxy)ethyl]-2-azetidinone-1-sulfonate (9f)** Prepared from **15f** (0.726 g, 0.84 mmol) as a white powder (0.285 g, 87%), $[\alpha]_D^{20}$ +155° ($c$=1.73, $H_2O$). IR (KBr): 3470, 2980, 1760, 1690, 1430, 1250 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 1.27 (3H, d, $J$=6.4 Hz, Me), 1.36 (3H, d, $J$=6.5 Hz, Me), 2.82 (4H, brs, $CH_2NHCH_2$), 2.94 (1H, dd, $J$=2.6, 6.6 Hz, $C_3$-H), 3.48—3.63 (4H, m, $CH_2N(CO)CH_2$), 4.05 (1H, dq, $J$=6.4, 6.6 Hz, HO-CH), 4.12 (1H, dd, $J$=2.6, 5.5 Hz, $C_4$-H), 5.17 (1H, dq, $J$=5.5, 6.5 Hz, CHOCO). MS (SIMS) $m/z$: 390 $(M+H)^+$, 428 $(M+K)^+$.

**Potassium (3*S*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-4-[(*S*)-1-(*N*-(pyridin-2-ylmethyl)carbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (9g)** Prepared from **15g** (0.322 g, 0.43 mmol) as a white powder (0.159 g, 90%), $[\alpha]_D^{20}$ −42.8° ($c$=1.65, $H_2O$). IR (KBr): 3400, 1760, 1710, 1540, 1260 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 1.27 (3H, d, $J$=6.3 Hz, Me), 1.38 (3H, d, $J$=6.5 Hz, Me), 2.99 (1H, dd, $J$=2.4, 6.2 Hz, $C_3$-H), 4.08 (1H, dq, $J$=6.2, 6.3 Hz, HO-CH), 4.16 (1H, dd, $J$=2.4, 5.0 Hz, $C_4$-H), 4.38 (1H, d, $J$=16.4 Hz, NCH), 4.45 (1H, d, $J$=16.4 Hz, NCH), 5.19 (1H, dq, $J$=5.0, 6.5 Hz, CHOCO), 7.28 (1H, dd, $J$=5.0, 7.7 Hz, $C_5$-H of the pyridine ring), 7.47 (1H, d, $J$=7.7 Hz, $C_3$-H of the pyridine ring), 7.81 (1H, ddd, $J$=1.7, 7.7, 7.7 Hz, $C_4$-H of the pyridine ring), 8.45 (1H, d, $J$=5.0 Hz, $C_6$-H of the pyridine ring). MS (SIMS) $m/z$: 455 $(M+K)^+$. *Anal.* Calcd for $C_{14}H_{18}KN_3O_7S\cdot0.25H_2O$: C, 40.42; H, 4.48; N, 10.10. Found: C, 40.40; H, 4.50; N, 9.87.

**Potassium (3*S*,4*S*)-4-[(*S*)-1-(*N*-Cyclopropylcarbamoyloxy)ethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone-1-sulfonate (9h)** Prepared from **15h** (0.391 g, 0.56 mmol) as a white powder (0.184 g, 91%), $[\alpha]_D^{20}$ −19.3° ($c$=1.63, $H_2O$). IR (KBr): 3400, 1760, 1710, 1540, 1260 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 0.40—0.70 (4H, m, $CH_2CH_2$), 1.26 (3H, d, $J$=6.6 Hz, Me), 1.35 (3H, d, $J$=6.4 Hz, Me), 2.39—2.59 (1H, m, NCH), 2.94 (1H, dd, $J$=2.4, 6.2 Hz, $C_3$-H), 3.98—4.30 (2H, m, $C_4$-H and CHOCO), 5.06—5.24 (1H, m, HO-CH). MS (SIMS) $m/z$: 361 $(M+H)^+$, 399 $(M+K)^+$. *Anal.* Calcd for $C_{11}H_{17}KN_2O_7S\cdot H_2O$: C, 34.91; H, 5.06; N, 7.40. Found: C, 34.97; H, 5.11; N, 7.40.

**Potassium (3*S*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-4-[(*S*)-1-(*N*-(2-hydroxyethyl)carbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (9i)** Prepared from **15i** (0.776 g, 0.93 mmol) as a white powder (0.298 g, 88%), $[\alpha]_D^{20}$ −19.2° ($c$=1.20, $H_2O$). IR (KBr): 3420, 2980, 1760, 1710, 1530, 1260 $cm^{-1}$. $^1$H-NMR ($CD_3OD$–$D_2O$) $\delta$: 1.36 (3H, d, $J$=6.4 Hz, Me), 1.28 (3H, d, $J$=6.4 Hz, Me), 3.04 (1H, dd, $J$=2.5, 5.8 Hz, $C_3$-H), 3.20—3.30 (2H, m, $NCH_2CH_2O$), 3.56—3.65 (2H, m, $NCH_2CH_2O$), 4.12 (1H, dq, $J$=5.8, 6.4 Hz, HO-CH). 4.16 (1H, dd, $J$=2.5, 5.2, $C_4$-H), 5.13 (1H, dq, $J$=5.2, 6.4 Hz, CHOCO). MS (SIMS) $m/z$: 365 $(M+H)^+$, 403 $(M+K)^+$. *Anal.* Calcd for $C_{10}H_{17}KN_2O_8S\cdot0.5H_2O$: C, 32.16; H, 4.86; N, 7.50. Found: C, 31.97; H, 4.88; N, 7.56.

**Potassium (3*S*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-4-[(*S*)-1-(*N*-phenylcarbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (9j)** Prepared from **15j** (0.400 g, 0.55 mmol) as a white powder (0.117 g, 89%), $[\alpha]_D^{20}$ −25.4° ($c$=1.22, $H_2O$). IR (KBr): 3450, 3370, 1760, 1710, 1610, 1530, 1450, 1235 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 1.28 (3H, d, $J$=6.4 Hz, Me), 1.43 (3H, d, $J$=6.4 Hz, Me), 3.02 (1H, dd, $J$=2.6, 6.4 Hz, $C_3$-H), 4.08 (1H, dq, $J$=each 6.4 Hz, HO-CH), 4.20 (1H, dd, $J$=2.6, 4.9 Hz, $C_4$-H), 5.26 (1H, dq, $J$=4.9, 6.4 Hz, CHOCO), 7.00 (1H, t, $J$=7.4 Hz, $C_4$-H of the benzene ring), 7.26 (2H, dd, $J$=7.4, 7.9 Hz, $C_3$-H and $C_5$-H of the benzene ring), 7.41 (2H, d, $J$=7.9 Hz, $C_2$-H and $C_6$-H of the benzene ring). MS (SIMS) $m/z$: 435 $(M+K)^+$. *Anal.* Calcd for $C_{14}H_{17}KN_2O_7S\cdot0.25H_2O$: C, 41.93, H, 4.40; N, 6.99. Found: C, 41.78; H, 4.18; N, 6.93.

**Potassium (3*S*,4*S*)-4-[(*S*)-1-(*N*-(4-Fluorophenyl)carbamoyloxy)ethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone-1-sulfonate (9k)** Prepared from **15k** (0.641 g, 0.85 mmol) as a white powder (0.286 g, 88%), $[\alpha]_D^{20}$ −26.6° ($c$=1.62, $H_2O$). IR (KBr): 3450, 3360, 1755, 1610, 1535, 1230 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 1.28 (3H, d, $J$=6.4 Hz, Me), 1.42 (3H, d, $J$=6.4 Hz, Me), 3.00 (1H, dd, $J$=2.6, 6.4 Hz, $C_3$-H), 4.07 (1H, dq, $J$=each 6.4 Hz, HO-CH), 4.19 (1H, dd, $J$=2.6, 5.0 Hz, $C_4$-H), 5.24 (1H, dq, $J$=5.0, 6.4 Hz, CHOCO), 6.96—7.02 (2H, m, $C_3$-H and $C_5$-H of the benzene ring), 7.39—7.43 (2H, m, $C_2$-H and $C_6$-H of the benzene ring). MS (SIMS) $m/z$: 453 $(M+K)^+$. *Anal.* Calcd for $C_{14}H_{16}FKN_2O_7S$: C, 40.57; H, 3.89; N, 6.76. Found: C, 40.42; H, 3.69; N, 6.84.

**Dipotassium (3*S*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-4-[(*S*)-1-(*N*-methoxy-*N*-sulfonatocarbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (9l) and Potassium (3*S*,4*S*)-3-[(*R*)-1-Hydroxyethyl]-4-[(*S*)-1-(*N*-methyloxy-*N*-sulfonatocarbamoyloxy)ethyl]-2-azetidinone (18)** A mixture of **14l** (0.110 g, 0.35 mmol) and $SO_3$–Py (0.111 g, 0.70 mmol) in DMF (0.6 ml) was stirred at 50 °C for 1 h. Tetrabutylammonium hydrogensulfate (0.238 g, 0.70 mmol) and 0.5 M $KH_2PO_4$ (15 ml) were added, and the mixture was extracted with $CH_2Cl_2$. The dichloromethane extracts were combined and dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave an oily residue which was separated by column chromatography ($SiO_2$, AcOEt–MeOH (10 : 1)) to afford the diammonium salt (**15l**) as a colorless oil (0.146 g, 41%) from the more polar fraction and the monoammonium salt (**17**) as a colorless oil (88 mg, 36%) from the less polar fraction. These two compounds were immediately converted to **9l** and **18**, respectively. The same treatments of **15l** (89 mg, 0.087 mmol) and **17** (52 mg, 0.074 mmol) as described for the preparation of **9a**, gave **9l** (36.4 mg, 89%) and **18** (23.1 mg, 89%) both as a white powder. **9l**: $[\alpha]_D^{20}$ +1.3° ($c$=1.35, $H_2O$). IR (KBr): 3500, 2980, 2940, 1760, 1250 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 1.38 (3H, d, $J$=6.4, Me), 1.44 (3H, d, $J$=6.4 Hz, Me), 3.22 (1H, dd, $J$=2.7, 6.0 Hz, $C_3$-H), 3.66 (3H, s, OMe), 4.27 (1H, dd, $J$=2.7, 5.1 Hz, $C_4$-H), 4.76 (1H, dq, $J$=6.0, 6.4 Hz, HO-CH), 5.26 (1H, dq, $J$=5.1, 6.4 Hz, CHOCO). MS (SIMS) $m/z$: 507 $(M+K)^+$. *Anal.* Calcd for $C_9H_{14}K_2N_2O_{11}S\cdot0.75H_2O$: C, 22.42; H, 3.24; N, 5.81. Found: C, 22.65; H, 3.28; N, 6.02. **18**: IR (KBr): 3470, 3260, 2970, 1750, 1250 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 1.33 (3H, d, $J$=6.4 Hz, Me), 1.45 (3H, d, $J$=6.3 Hz, Me), 3.02 (1H, dd, $J$=2.2, 8.4 Hz, $C_3$-H), 3.66 (3H, s, OMe), 3.80 (1H, dd, $J$=2.2, 6.4 Hz, $C_4$-H), 4.66 (1H, dq, $J$=6.3, 8.3, HO-CH), 4.89 (1H, dq, $J$=each 6.4 Hz, CHOCO). MS (SIMS) $m/z$: 351 $(M+H)^+$, 389 $(M+K)^+$.

**Potassium (3*S*,4*S*)-4-[(*S*)-1-(*N*-Benzyl-*N*-methoxycarbamoyloxy)ethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone-1-sulfonate (9m)** Prepared from **15m** (0.188 g, 0.24 mmol) as a white powder (91 mg, 86%), $[\alpha]_D^{20}$ −4.7°

($c$=1.24, $H_2O$). IR (KBr): 3450, 3000, 1760, 1710, 1380, 1240 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 1.24 (3H, d, $J$=6.4 Hz, Me), 1.40 (3H, d, $J$=6.4 Hz, Me), 2.94 (1H, dd, $J$=2.6, 6.4 Hz, $C_3$-H), 3.60 (3H, s, OMe), 4.03 (1H, dq, $J$=each 6.4 Hz, HO-CH), 4.17 (1H, dd, $J$=2.6, 4.7 Hz, $C_4$-H), 4.63 (1H, d, $J$=15.7 Hz, NCH), 4.77 (1H, d, $J$=15.7 Hz, NCH), 5.26 (1H, dq, J=4.7, 6.4, CHOCO), 7.26—7.36 (5H, m, $C_6H_5$). MS (SIMS) $m/z$: 441 $(M+H)^+$, 479 $(M+K)^+$. *Anal.* Calcd for $C_{16}H_{21}KN_2O_8S \cdot 0.5H_2O$: C, 42.75; H, 4.93; N, 6.23. Found: C, 42.59; H, 5.10; N, 6.09.

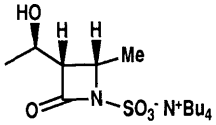
**Potassium (3*S*,4*S*)-4-[(*S*)-1-(*N*-Benzyl-*N*-benzyloxycarbamoyloxy)-ethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone-1-sulfonate (9n)** Prepared from **15n** (0.312 g, 0.37 mmol) as a white powder (0.168 g, 88%). $^1$H-NMR ($CD_3OD$) $\delta$: 1.22 (3H, d, $J$=6.4 Hz, Me), 1.41 (3H, d, $J$=6.5 Hz, Me), 2.94 (1H, dd, $J$=2.6, 6.4 Hz, $C_3$-H), 4.03 (1H, dq, $J$=each 6.4 Hz, HO-CH), 4.19 (1H, dd, $J$=2.6, 4.7 Hz, $C_4$-H), 4.57 (1H, d, $J$=15.6 Hz, NCH), 4.70 (1H, d, $J$=15.6 Hz, NCH), 4.79 (2H, s, $OCH_2$), 5.28 (1H, dq, $J$=4.7, 6.5 Hz, CHOCO), 7.26—7.35 (10H, m, $2 \times C_6H_5$).

**Potassium (3*S*,4*S*)-4-[(*S*)-1-(*N*-Benzyl-*N*-hydoxycarbamoyloxy)ethyl]-3-[(*R*)-1-hydroxyethyl]-2-azetidinone-1-sulfonate (9o)**[17] A mixture of **9n** (0.113 g, 0.22 mmol) and 20% $Pd(OH)_2$ on carbon (15 mg) in MeOH–$H_2O$ (2:1, 3 ml) was stirred at room temperature for 6 h under hydrogen at 2 atm pressure. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was lyophilized to give **9o** as a white powder (92 mg, quantitative yield), $[\alpha]_D^{20}$ −9.4° ($c$=1.62, $H_2O$). IR (KBr): 3440, 2980, 1760, 1710, 1450, 1240 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 1.24 (3H, d, $J$=6.5 Hz, Me), 1.40 (3H, d, $J$=6.5 Hz, Me), 2.96 (1H, dd, $J$=2.6, 6.4 Hz, $C_3$-H), 4.04 (1H, dq, $J$=6.4, 6.5 Hz, HO-CH), 4.14 (0.3H, dd, $J$=2.6, 4.8 Hz, $C_4$-H), 4.17 (0.7H, dd, $J$=2.6, 5.1 Hz, $C_4$-H), 4.63 (1H, d, $J$=15.6 Hz, NCH), 4.76 (1H, d, $J$=15.6 Hz, NCH), 5.20 (0.3H, dq, $J$=4.8, 6.5 Hz, CHOCO), 5.22 (0.7H, dq, $J$=5.1, 6.5, CHOCO), 7.23—7.36 (5H, m, $C_6H_5$).[17] MS (SIMS) $m/z$: 427 $(M+H)^+$, 465 $(M+K)^+$. *Anal.* Calcd for $C_{15}H_{19}KN_2O_8S \cdot 0.5H_2O$: C, 41.37; H, 4.62; N, 6.43. Found: C, 41.22; H, 4.75; N, 6.29.

**Acknowledgment** The authors are grateful to Drs. S. Suzue and K. Hirai, Central Research Laboratories, Kyorin Pharmaceutical Co., Ltd., for evaluating *in vitro* antibacterial activity.

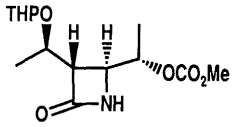
**References and Notes**

1) Visiting scientist from the Central Research Laboratories, Kyorin Pharmaceutical Co., Ltd.
2) R. B. Sykes, C. M. Cimarusti, D. P. Bonner, K. Bush, D. M. Floyd, N. H. Georgopapadakou, W. H. Koster, W. C. Liu, W. L. Parker, P. A. Principe, M. L. Rathnum, W. A. Slusarchyk,, W. H. Trejo, and J. S. Wells, *Nature* (London), **291**, 489 (1981).
3) A. Imada, K. Kitano, K. Kintaka, M. Muroi, and M. Asai, *Nature* (London), **289**, 590 (1981).
4) C. M. Cimarusti and R. B. Sykes, *Chem. Brit.*, **25**, 371 (1989).
5) R. B. Sykes, D. P. Bonner, K. Bush and N. H. Georgopapadakou, *Antimicrob. Agents Chemother.*, **21**, 85 (1982).
6) M. Sendai, S. Hashiguchi, M. Tomimoto, S. Kishimoto, T. Matsuo, M. Kondo, and M. Ochiai, *J. Antibiot.*, **38**, 346 (1985).
7) W. J. Leanza, K. J. Wildonger, T. W. Miller, and B. G. Christensen, *J. Med. Chem.*, **22**, 1435 (1979); B. G. Christensen, *Chem. Brit.*, **25**, 371 (1989).
8) Y. Ito, T. Kawabata and S. Terashima, *Tetrahedron Lett.*, **27**, 5751 (1986); Y. Ito, Y. Kobayashi, T. Kawabata, M. Takase, and S. Terashima, *Tetrahedron*, **45**, 5767 (1989).
9) Synthesis of the racemic monobactam (i) which bears an (*R**)-1-hydroxyethyl group at the $C_3$-position and has $C_{3,4}$-*cis*-configuration has recently been reported. Antibacterial testing showed i to possess no antibacterial activity. C. J. Ashcroft, J. Brennan, C. E. Newall, and S. M. Roberts, *Tetrahedron Lett.*, **25**, 877 (1984).




i

10) When we attempted to react the methyl carbonate (ii), prepared by treating **11** with methyl chloroformate in the presence of DMAP, with an excess of ammonia, **11** was recovered (K. Obi, Y. Ito, and S. Terashima, unpublished results). Accordingly, we chose an active mixed carbonate such as **12** for obtaining **13**.




ii

11) F. M. Hershenson, *J. Org. Chem.*, **40**, 1260 (1975).
12) W. O. Foye and I. E. Fedor, Jr., *J. Am. Pharm. Assoc.*, **48**, 412 (1959).
13) Among **9d**—**k** produced, **9e** was found to consist of two conformers or two diastereomers based on the NMR spectrum (see Experimental).
14) In the NMR spectra of **18** and **9l**, the $C_4$-protons appear at 3.80 and 4.27 ppm, respectively. Since the signal of the $C_4$-proton involved in **14l**, which gave **17** and **15l**, appeared at 3.73 ppm, the structures of **18** and **9l** and those of **17** and **15l** could be assigned as shown.
15) P. C. Bernhart and C.-G. Wermuth, *Tetrahedron Lett.*, **15**, 2493 (1974).
16) K. Kurita, T. Matsumura and Y. Iwakura, *J. Org. Chem.*, **41**, 2070 (1976).
17) Based on the NMR spectrum, **9o** was anticipated to consist of two conformers or two diastereomers (see Experimental).
18) Minimum inhibitory concentration.