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

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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 β -lactam antibiotics classified afterwards as monobactams were independently discovered by research groups at Squibb²⁾ and Takeda.³⁾ Since then, numerous chemical modifications of those natural antibiotics have been studied extensively at the C₃-amido side chain and C₄-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 C₆-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 β -lactam (**8**) carry-

ing an (*R*)-1-hydroxyethyl group at the C₃-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 C₄-side chain of **8**, the (*R*)-1-hydroxyethyl group present at

Chart 1

Chart 2

the C₃-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 (SO₃-Py)^{5,6} followed by treatment with tetrabutylammonium 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

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 (**14i**) was synthesized from **12** and methoxyamine similarly to **14a–c**, as shown in Chart 4. Sulfonation of **14i** as done for **14a–c** was found to produce the mono- and the diammonium salts (**17** and **15i**) in 36% and 41% yields, respectively. The structures of these salts could be assigned at the stages of **18** and **9i** 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 **15i**) were directly derived to the mono- and the dipotassium salts (**18** and **9i**) 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-methoxyamine¹⁵ 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 carbamoyloxy 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. ¹H-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.

(3S,4S)-4-[(S)-1-Benzoyloxyethyl]-3-[(R)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (10) A mixture of (3S,4S)-4-[(S)-1-benzoyloxyethyl]-3-[(R)-1-hydroxyethyl]-2-azetidinone (**8**)⁶ (1.00 g, 4.01 mmol), 3,4-dihydro-2H-pyran (1.83 ml, 20.1 mmol), and pyridinium *p*-toluene-

sulfonate (60 mg) in CH₂Cl₂ (10 ml) was stirred at room temperature for 2 h, and then diluted with CH₂Cl₂ (30 ml). The organic layer was washed successively with H₂O and saturated NaCl, then dried over anhydrous MgSO₄. Filtration and concentration *in vacuo* gave an oily residue, which was purified by column chromatography (SiO₂, hexane–AcOEt (7:3)) to give **8** as a colorless oil (1.31 g, 98%). IR (neat): 2950, 1760 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.24 (3H, d, *J* = 5.9 Hz, CH₃), 1.33 (3H, d, *J* = 6.4 Hz, CH₃), 1.47–1.73 (6H, m, (CH₂)₃), 2.77–2.85 (1H, m, C₃-H), 3.41–3.60 (4H, m, C₄-H, CHO-THP and OCH₂), 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, brs, OCHO), 6.07 (1H, brs, NH), 7.32 (5H, s, C₆H₅). MS *m/z*: 248 (M – THP)⁺.

(3S,4S)-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 1N 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. ¹H-NMR (CDCl₃) δ : 1.25 (1.5H, d, *J* = 6.2 Hz, CH₃CHO-THP), 1.27 (1.5H, d, *J* = 6.2 Hz, CH₃CHO-THP), 1.35 (3H, d, *J* = 6.8 Hz, CH₃CHO), 1.41–1.80 (6H, m, (CH₂)₃), 2.93 (1H, dd, *J* = 2.2, 5.5 Hz, C₃-H), 3.42–4.10 (5H, m, C₄-H, 2 × CHO and OCH₂), 4.72 (1H, brs, OCHO), 6.17 (1H, brs, NH). MS *m/z*: 244 (M + 1)⁺, 142 (M – THPO)⁺.

(3S,4S)-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 H₂O and saturated NaCl, then dried over anhydrous MgSO₄. Filtration and concentration *in vacuo* followed by purification by column chromatography (SiO₂, CH₂Cl₂–AcOEt (3:1)) gave **12** as a pale yellow caramel (6.25 g, 97%). IR (neat): 2750, 1760, 1710, 1530, 1220 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.29 (1.5H, d, *J* = 6.6 Hz, CH₃CHO-THP), 1.38 (1.5H, d, *J* = 6.6 Hz, CH₃CHO-THP), 1.48 (1.5H, d, *J* = 6.4 Hz, CH₃CHO), 1.62 (1.5H, d, *J* = 6.4 Hz, CH₃CHO), 1.58–1.83 (6H, m, (CH₂)₃), 2.89–3.02 (1H, m, C₃-H), 3.42–3.56 (1H, m, C₄-H), 3.77–3.92 (2H, m, OCH₂), 4.13 (1H, dq, *J* = each 6.6 Hz, THP-OCH), 4.73 (1H, brs, OCHO), 4.87 (1H, dq, *J* = each 6.4 Hz, CHOCO), 6.24 (1H, brs, NH), 7.39, 8.29 (4H, two d, *J* = each 9.2 Hz, C₆H₄). MS *m/z*: 270 (M – NO₂ – C₆H₄O)⁺.

(3S,4S)-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 (SiO₂, hexane–AcOEt (3:7)) to give **13a** as a colorless oil (0.099 g, 89%). ¹H-NMR (CDCl₃) δ : 1.23–1.84 (12H, m, 2 × CH₃ and (CH₂)₃), 2.88–2.97 (1H, m, C₃-H), 3.49–3.87 (2H, m, OCH₂), 3.78 (1H, dd, *J* = 2.2, 6.6 Hz, C₄-H), 3.98–4.24 (1H, m, THP-OCH), 4.71 (1H, brs, OCHO), 4.76 (1H, dq, *J* = each 6.6 Hz, CHOCO), 6.08 (1H, brs, NH). The

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

(3S,4S)-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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.22 (12H, m, $2 \times \text{CH}_3$ and $(\text{CH}_2)_3$), 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, $J=\text{each } 6.6$ Hz, CHOCO), 6.15 (1H, br s, NH and OCHO). MS m/z : 199 ($\text{M}-\text{THPO}$) $^+$.

(3S,4S)-4-[(S)-1-(N,N-Dimethylcarbamoyloxy)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%). $^1\text{H-NMR}$ (CDCl_3) δ : 1.22–1.89 (12H, m, $2 \times \text{CH}_3$ and $(\text{CH}_2)_3$), 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, $J=\text{each } 6.4$ Hz, CHOCO), 6.21 (1H, br s, NH).

(3S,4S)-4-[(S)-1-(N-Benzoyloxycarbonylmethyl)carbamoyloxy]ethyl]-3-[(R)-1-tetrahydropyran-2-yloxyethyl]-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 $^\circ\text{C}$. 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.22–1.78 (12H, m, $2 \times \text{CH}_3$ and $(\text{CH}_2)_3$), 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, $J=\text{each } 6.6$ 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 ($\text{M}-\text{THP}$) $^+$, 333 ($\text{M}-\text{THPO}$) $^+$. The carbamates (**13e, l**) were prepared from **12** in a similar manner to that described above.

(3S,4S)-4-[(S)-1-(N-Benzoyloxycarbonylmethyl-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*-methylglycinate¹¹) (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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.22–1.79 (12H, m, $2 \times \text{CH}_3$ and $(\text{CH}_2)_3$), 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 ($\text{M}+1$) $^+$.

(3S,4S)-4-[(S)-1-(4-Benzoyloxycarbonylpiperazin-1-yl)carbamoyloxy]ethyl]-3-[(R)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (13f) 1-Benzoyloxycarbonylpiperazine¹²⁾ (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 $^\circ\text{C}$, 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.22–1.80 (12H, m, $2 \times \text{CH}_3$ and $(\text{CH}_2)_3$), 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, $J=\text{each } 6.6$ 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 ($\text{M}-\text{THP}$) $^+$. The carbamates (**13g–i**) were prepared in a similar manner to that described above.

(3S,4S)-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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.22–1.86 (12H, m, $2 \times \text{CH}_3$ and $(\text{CH}_2)_3$), 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, $J=\text{each } 6.6$ 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 ($\text{M}-\text{THPO}$) $^+$.

(3S,4S)-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} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.45–0.85 (4H, m, CH_2CH_2), 1.24–1.81 (12H, m,

$2 \times \text{CH}_3$ and $(\text{CH}_2)_3$), 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 ($\text{M}+1$) $^+$, 225 ($\text{M}-\text{THPO}$) $^+$.

(3S,4S)-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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.22–1.80 (12H, m, $2 \times \text{CH}_3$ and $(\text{CH}_2)_3$), 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 $\text{NCH}_2\text{CH}_2\text{O}$), 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 ($\text{M}-\text{THP}$) $^+$, 229 ($\text{M}-\text{THPO}$) $^+$.

(3S,4S)-4-[(S)-1-(N-Methoxycarbamoyloxy)ethyl]-3-[(R)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (13l) 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.23–1.82 (12H, m, $2 \times \text{CH}_3$ and $(\text{CH}_2)_3$), 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 ($\text{M}-\text{THPO}$) $^+$.

(3S,4S)-4-[(S)-1-(N-Benzyl-N-benzoyloxycarbamoyloxy)ethyl]-3-[(R)-1-tetrahydropyran-2-yloxyethyl]-2-azetidinone (13n) Trichloromethyl chloroformate¹⁶⁾ (80 μl , 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 $^\circ\text{C}$ under an argon atmosphere.¹⁶⁾ The mixture was stirred at the same temperature for 1.5 h. A solution of *N*-benzyl benzoyloxylamine¹³⁾ (0.629 g, 2.95 mmol) in CH_2Cl_2 (2 ml) was added to the reaction mixture at 0 $^\circ\text{C}$. 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.25–1.82 (12H, m, $2 \times \text{CH}_3$ and $(\text{CH}_2)_3$), 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, $2 \times \text{C}_6\text{H}_5$). MS m/z : 482 (M) $^+$.

(3S,4S)-3-[(R)-1-(Benzoyloxycarbonyloxy)ethyl]-4-[(S)-1-carbamoyloxyethyl]-2-azetidinone (14a) A mixture of **13a** (0.212 g, 0.74 mmol) and methanolic 1N 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. Benzoyloxycarbonyl 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 $^\circ\text{C}$. 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 , 0.5N 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 $_2\text{O}$ gave an analytical sample of **14a** as colorless needles, mp 137–139 $^\circ\text{C}$ and $[\alpha]_D^{20} +11.6^\circ$ ($c=0.92$, CHCl_3). IR (KBr): 3470, 3280, 1750, 1690, 1270 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.21 (3H, d, $J=6.6$ Hz, Me), 1.43 (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, $J=2.4$, 6.8 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 ($\text{M}-\text{ZO}$) $^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_6$: 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.

(3S,4S)-3-[(R)-1-(Benzoyloxycarbonyloxy)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} . $^1\text{H-NMR}$ (CDCl_3) δ : 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 ($\text{M}-\text{ZO}$) $^+$.

(3S,4S)-3-[(R)-1-(Benzoyloxycarbonyloxy)ethyl]-4-[(S)-1-N,N-dimethylcarbamoyloxyethyl]-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} . $^1\text{H-NMR}$ (CDCl_3) δ : 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, PhCH₂ and Z-OCH), 6.00 (1H, br s, NH), 7.36 (5H, s, Ph). MS *m/z*: 365 (M)⁺, 213 (M–151)⁺.

(3S,4S)-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. ¹H-NMR (CDCl₃) δ: 1.20 (3H, d, *J* = 6.4 Hz, Me), 1.44 (3H, d, *J* = 6.4 Hz, Me), 2.95–3.11 (1H, m, C₃-H), 3.63 (1H, dd, *J* = 2.2, 6.8 Hz, C₄-H), 3.95 (2H, d, *J* = 5.7 Hz, NCH₂COO), 4.83 (1H, dq, *J* = 6.4, 6.8 Hz, CHOCO), 5.01–5.29 (6H, m, NH, Z-OCH and 2 × PhCH₂), 6.11 (1H, br s, NH), 7.35 (10H, s, 2 × Ph). MS *m/z*: 407 (M–Ph)⁺, 333 (M–ZO)⁺.

(3S,4S)-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. ¹H-NMR (CDCl₃) δ: 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, C₃-H), 3.60–3.72 (1H, m, C₄-H), 4.05 (2H, s, NCH₂COO), 4.74–4.89 (1H, m, CHOCO), 5.03–5.22 (5H, m, 2 × PhCH₂ and Z-OCH), 6.03 (1H, br s, NH), 7.35 (10H, s, 2 × Ph). MS *m/z*: 498 (M)⁺, 347 (M–ZO)⁺.

(3S,4S)-3-[(R)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(S)-1-((4-benzyl-oxycarbonylpiperazin-1-yl)carbamoyloxy)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. ¹H-NMR (CDCl₃) δ: 1.22 (3H, d, *J* = 6.2 Hz, Me), 1.44 (3H, d, *J* = 6.4 Hz, Me), 2.97–3.10 (1H, m, C₃-H), 3.44 (8H, s, piperazine), 3.67 (1H, dd, *J* = 2.4, 6.6 Hz, C₄-H), 4.85 (1H, dq, *J* = 6.4, 6.6 Hz, CHOCO), 5.03–5.34 (5H, m, 2 × PhCH₂ and ZOCH), 6.08 (1H, br s, NH), 7.35 (10H, s, 2 × C₆H₅). MS *m/z*: 539 (M)⁺, 388 (M–Z)⁺.

(3S,4S)-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. ¹H-NMR (CDCl₃) δ: 1.22 (3H, d, *J* = 6.4 Hz, Me), 1.44 (3H, d, *J* = 6.4 Hz, Me), 2.98–3.08 (1H, m, C₃-H), 3.63 (1H, dd, *J* = 2.2, 7.3 Hz, C₄-H), 4.45 (2H, d, *J* = 5.5 Hz, NCH₂COO), 4.84 (1H, dq, *J* = 6.4, 7.3 Hz, CHOCO), 4.96–5.26 (3H, m, PhCH₂ and Z-OCH), 5.87 (1H, br s, NH), 6.45 (1H, br s, NH), 7.12–7.26 (2H, m, C₃-H and C₅-H of the pyridine ring), 7.35 (5H, s, C₆H₅), 7.57–7.76 (1H, m, C₄-H of the pyridine ring), 8.53 (1H, d, *J* = 4.8 Hz, C₆-H of the pyridine ring). MS *m/z*: 427 (M)⁺, 276 (M–ZO)⁺.

(3S,4S)-3-[(R)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(S)-1-(N-cyclopropylcarbamoyloxy)ethyl]-2-azetidinone (14h) Prepared from **13h** (0.336 g, 1.03 mmol) as a colorless oil (0.314 g, 81%). IR (neat): 3300, 3030, 1760, 1510, 1390, 1260 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.44–0.83 (4H, m, CH₂CH₂), 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, C₃-H), 3.64 (1H, dd, *J* = 2.5, 6.6 Hz, C₄-H), 4.66–5.19 (5H, m, CHOCO, Z-OCH, PhCH₂ and NH), 6.02 (1H, br s, NH), 7.36 (5H, s, C₆H₅). MS *m/z*: 376 (M)⁺, 225 (M–ZO)⁺.

(3S,4S)-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. ¹H-NMR (CDCl₃) δ: 1.19 (3H, d, *J* = 6.6 Hz, Me), 1.44 (3H, d, *J* = 6.4 Hz, Me), 2.95–3.08 (1H, m, C₃-H), 3.33–3.51 (2H, m, NCH₂CH₂O), 3.59 (1H, dd, *J* = 2.2, 7.0 Hz, C₄-H), 4.16–4.29 (2H, m, NCH₂CH₂O), 4.73–5.29 (6H, m, CHOCO, Z-OCH and 2 × PhCH₂), 6.05 (1H, br s, NH), 7.35 (5H, s, C₆H₅), 7.37 (5H, s, Ph). MS *m/z*: 514 (M)⁺.

(3S,4S)-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, H₂O, and saturated NaCl, then dried over anhydrous MgSO₄. 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 H₂O and saturated NaCl, then dried over anhydrous MgSO₄. Filtration and concentration *in vacuo* followed by column chromatography (SiO₂, 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 CH₂Cl₂ (11 ml) at 0 °C.

After being stirred at room temperature for 16 h, the mixture was diluted with CH₂Cl₂ (60 ml). The organic layer was separated, washed successively with H₂O and saturated NaCl, then dried over anhydrous MgSO₄. Filtration and concentration *in vacuo* gave an oily residue which was purified by column chromatography (SiO₂, 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. ¹H-NMR (CDCl₃) δ: 1.27 (3H, d, *J* = 6.4 Hz, Me), 1.44 (3H, d, *J* = 6.4 Hz, Me), 3.03–3.14 (1H, m, C₃-H), 3.70 (1H, dd, *J* = 2.4, 6.6 Hz, C₄-H), 4.84–5.27 (4H, m, CHOCO, Z-OCH and PhCH₂), 6.23 (1H, br s, NH), 6.76 (1H, br s, NH), 7.23–7.35 (10H, m, 2 × C₆H₅). MS *m/z*: 412 (M)⁺.

(3S,4S)-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. ¹H-NMR (CDCl₃) δ: 1.27 (3H, d, *J* = 6.4 Hz, Me), 1.44 (3H, d, *J* = 6.2 Hz, Me), 3.02–3.15 (1H, m, C₃-H), 3.70 (1H, dd, *J* = 2.4, 6.6 Hz, C₄-H), 4.84–5.20 (4H, m, CHOCO, Z-OCH and PhCH₂), 6.22 (1H, br s, NH), 6.74 (1H, br s, NH), 6.88–7.39 (4H, m, C₆H₄F), 7.35 (5H, s, C₆H₅). MS *m/z*: 430 (M)⁺.

(3S,4S)-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. ¹H-NMR (CDCl₃) δ: 1.32 (3H, d, *J* = 6.4 Hz, Me), 1.41 (3H, d, *J* = 6.6 Hz, Me), 2.88–3.00 (1H, m, C₃-H), 3.73 (1H, dd, *J* = 2.2, 5.9 Hz, C₄-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, PhCH₂), 6.13 (1H, br s, NH), 7.39 (6H, s, C₆H₅ and NH). MS *m/z*: 366 (M)⁺.

(3S,4S)-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 CH₂Cl₂ (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*-benzylmethoxyamine¹⁵⁾ (0.552 g, 4.03 mmol) in CH₂Cl₂ (3 ml) was added to the reaction mixture. The mixture was stirred at 0 °C for 0.5 h, then diluted with CH₂Cl₂ (100 ml). The dichloromethane solution was washed successively with H₂O and saturated NaCl, then dried over anhydrous MgSO₄. Filtration and concentration *in vacuo* followed by column chromatography (SiO₂, 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 H₂O and saturated NaCl, then dried over anhydrous MgSO₄. 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 CH₂Cl₂ (11 ml) at 0 °C. After being stirred at room temperature for 18 h, the mixture was diluted with CH₂Cl₂ (80 ml). The dichloromethane solution was washed successively with H₂O and saturated NaCl, then dried over anhydrous MgSO₄. Filtration and concentration *in vacuo* followed by purification by column chromatography (SiO₂, 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. ¹H-NMR (CDCl₃) δ: 1.23 (3H, d, *J* = 6.4 Hz, Me), 1.41 (3H, d, *J* = 6.4 Hz, Me), 2.90–3.03 (1H, m, C₃-H), 3.54–3.67 (1H, m, C₄-H), 3.60 (3H, s, OMe), 4.61 (2H, s, NCH₂Ph), 4.74–5.23 (4H, m, CHOCO, Z-OCH and PhCH₂), 5.82 (1H, br s, NH), 7.31 (5H, s, C₆H₅), 7.35 (5H, s, C₆H₅). MS *m/z*: 305 (M–ZO)⁺.

(3S,4S)-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. ¹H-NMR (CDCl₃) δ: 1.20 (3H, d, *J* = 6.4 Hz, Me), 1.41 (3H, d, *J* = 6.4 Hz, Me), 2.88–3.01 (1H, m, C₃-H), 3.55 (1H, dd, *J* = 2.4, 7.5 Hz, C₄-H), 4.56 (2H, s, NCH₂Ph), 4.73 (2H, s, OCH₂Ph), 4.69–5.19 (4H, m, CHOCO, Z-OCH and PhCH₂), 5.54 (1H, br s, NH), 7.32 (10H, s, 2 × C₆H₅), 7.35 (5H, s, C₆H₅). MS *m/z*: 532 (M)⁺, 381 (M–ZO)⁺.

Tetrabutylammonium (3S,4S)-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 SO₃–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 KH₂PO₄ (15 ml) were added, and the mixture was extracted with CH₂Cl₂. The dichloromethane extracts were combined and dried over anhydrous MgSO₄. Filtration and concentration *in vacuo* gave an oily residue, which

was purified by column chromatography (SiO₂, 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. ¹H-NMR (CDCl₃) δ: 0.98 (12H, t, 4 × (CH₂)₃CH₃), 1.25–1.71 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 3.05 (1H, dd, *J* = 2.6, 6.4 Hz, C₃-H), 3.15–3.33 (8H, m, 4 × CH₂CH₂CH₂CH₃), 4.04 (1H, dd, *J* = 2.6, 4.4 Hz, C₄-H), 4.64 (2H, br s, NH₂), 4.93–5.29 (4H, m, CHOCO, Z-OCH and PhCH₂), 7.35 (5H, s, C₆H₅). The ammonium salts (**15b–k**, **m**, **n**) were prepared in the same manner as described above.

Tetrabutylammonium (3S,4S)-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. ¹H-NMR (CDCl₃) δ: 0.99 (12H, t, 4 × (CH₂)₃CH₃), 1.24–1.74 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 2.56 (3H, d, *J* = 4.8 Hz, NMe), 3.05 (1H, dd, *J* = 2.4, 6.6 Hz, C₃-H), 3.14–3.34 (8H, m, 4 × CH₂CH₂CH₂CH₃), 4.03 (1H, dd, *J* = 2.4, 4.6 Hz, C₄-H), 4.71 (1H, br s, NH), 4.97–5.29 (4H, m, CHOCO, Z-OCH and PhCH₂), 7.35 (5H, s, C₆H₅).

Tetrabutylammonium (3S,4S)-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. ¹H-NMR (CDCl₃) δ: 0.99 (12H, t, 4 × (CH₂)₃CH₃), 1.25–1.74 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 2.80 (6H, s, N(CH₃)₂), 3.08 (1H, dd, *J* = 2.4, 6.4 Hz, C₃-H), 3.14–3.35 (8H, m, 4 × CH₂CH₂CH₂CH₃), 4.05 (1H, dd, *J* = 2.4, 4.4 Hz, C₄-H), 4.95–5.35 (4H, m, CHOCO, Z-OCH and PhCH₂), 7.34 (5H, s, C₆H₅).

Tetrabutylammonium (3S,4S)-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. ¹H-NMR (CDCl₃) δ: 1.00 (12H, t, 4 × (CH₂)₃CH₃), 1.26–1.72 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 3.07–3.35 (9H, m, C₃-H and 4 × CH₂CH₂CH₂CH₃), 3.78 (2H, d, *J* = 5.7 Hz, NCH₂COO), 4.06 (1H, dd, *J* = 2.4, 4.8 Hz, C₄-H), 4.96–5.38 (7H, m, CHOCO, Z-OCH, 2 × PhCH₂ and NH), 7.34 (10H, s, 2 × C₆H₅).

Tetrabutylammonium (3S,4S)-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. ¹H-NMR (CDCl₃) δ: 0.99 (12H, t, 4 × (CH₂)₃CH₃), 1.25–1.74 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 2.88 (3H, s, NMe), 3.05 (1H, dd, *J* = 2.2, 6.6 Hz, C₃-H), 3.11–3.33 (8H, m, 4 × CH₂CH₂CH₂CH₃), 3.96–4.32 (3H, m, C₄-H and NCH₂COO), 4.98–5.37 (6H, m, CHOCO, Z-OCH and 2 × PhCH₂), 7.33 (10H, s, 2 × C₆H₅).

Tetrabutylammonium (3S,4S)-3-[(R)-1-(Benzyloxycarbonyloxy)ethyl]-4-[(S)-1-(4-benzyloxycarbonylpiperazin-1-yl)carbamoyloxy)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. ¹H-NMR (CDCl₃) δ: 0.99 (12H, t, 4 × (CH₂)₃CH₃), 1.23–1.73 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 3.08 (1H, dd, *J* = 2.2, 6.8 Hz, C₃-H), 3.16–3.51 (16H, m, piperazine and 4 × CH₂CH₂CH₂CH₃), 4.02 (1H, dd, *J* = 2.2, 5.7 Hz, C₄-H), 4.94–5.29 (6H, m, CHOCO, Z-OCH and 2 × PhCH₂), 7.32 (5H, s, C₆H₅), 7.33 (5H, s, C₆H₅).

Tetrabutylammonium (3S,4S)-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. ¹H-NMR (CDCl₃) δ: 0.99 (12H, t, 4 × (CH₂)₃CH₃), 1.23–1.73 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 3.08 (1H, dd, *J* = 2.6, 6.4 Hz, C₃-H), 3.16–3.35 (8H, m, 4 × CH₂CH₂CH₂CH₃), 4.10 (1H, dd, *J* = 2.6, 4.8 Hz, C₄-H), 4.38 (2H, d, NCH₂), 4.98–5.29 (4H, m, CHOCO, Z-OCH and PhCH₂), 5.68 (1H, br s, NH), 7.10–7.20 (2H, m, C₃-H and C₅-H of the pyridine ring), 7.29 (5H, s, C₆H₅), 7.62 (1H, ddd, *J* = 2.0, 7.7, 8.0 Hz, C₄-H of the pyridine ring), 8.48 (1H, d, *J* = 4.6 Hz, C₆-H of the pyridine ring).

Tetrabutylammonium (3S,4S)-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. ¹H-NMR (CDCl₃) δ: 0.41–0.75 (4H, m, CH₂CH₂), 1.00 (12H, t, 4 × (CH₂)₃CH₃), 1.26–1.74 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 2.44–2.57 (1H, m, NCH), 3.05 (1H, dd, *J* = 2.6, 9.0 Hz, C₃-H), 3.14–3.34 (8H, m, 4 × CH₂CH₂CH₂CH₃), 4.04 (1H, dd, *J* = 2.6, 5.1 Hz, C₄-H), 4.92–5.29 (5H, m, CHOCO, Z-OCH, PhCH₂ and NH), 7.35 (5H, s, C₆H₅).

Tetrabutylammonium (3S,4S)-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. ¹H-NMR (CDCl₃) δ: 0.99 (12H, t, 4 × (CH₂)₃CH₃), 1.25–1.79 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 2.99–3.46 (11H, m, C₃-H, 4 × CH₂CH₂CH₂CH₃ and NCH₂CH₂O), 4.00–4.16 (3H, m, C₄-H and NCH₂CH₂O), 4.95–5.45 (6H, m, CHOCO, Z-OCH and 2 × PhCH₂), 7.32 (5H, s, C₆H₅), 7.35 (5H, s, C₆H₅).

Tetrabutylammonium (3S,4S)-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. ¹H-NMR (CDCl₃) δ: 0.99 (12H, t, 4 × (CH₂)₃CH₃), 1.23–1.74 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 3.07 (1H, dd, *J* = 2.6, 6.8 Hz, C₃-H), 3.15–3.32 (8H, m, 4 × CH₂CH₂CH₂CH₃), 4.09 (1H, dd, *J* = 2.6, 5.5 Hz, C₄-H), 4.91–5.29 (4H, m, CHOCO, Z-OCH and PhCH₂), 7.29 (10H, s, 2 × C₆H₅).

Tetrabutylammonium (3S,4S)-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. ¹H-NMR (CDCl₃) δ: 0.98 (12H, t, 4 × (CH₂)₃CH₃), 1.25–1.72 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 3.04 (1H, dd, *J* = 2.4, 6.2 Hz, C₃-H), 3.14–3.32 (8H, m, 4 × CH₂CH₂CH₂CH₃), 4.08 (1H, dd, *J* = 2.4, 5.5 Hz, C₄-H), 4.94–5.26 (4H, m, CHOCO, Z-OCH and PhCH₂), 6.79–7.34 (4H, m, C₆H₄F), 7.30 (5H, s, C₆H₅).

Tetrabutylammonium (3S,4S)-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. ¹H-NMR (CDCl₃) δ: 0.99 (12H, t, 4 × (CH₂)₃CH₃), 1.26–1.74 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 3.06–3.36 (9H, m, C₃-H and 4 × CH₂CH₂CH₂CH₃), 3.52 (3H, s, OMe), 4.14 (1H, dd, *J* = 2.6, 5.9 Hz, C₄-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 PhCH₂), 7.27 (5H, s, C₆H₅), 7.32 (5H, s, C₆H₅).

Tetrabutylammonium (3S,4S)-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. ¹H-NMR (CDCl₃) δ: 0.98 (12H, t, 4 × (CH₂)₃CH₃), 1.25–1.72 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 3.06 (1H, dd, *J* = 2.4, 5.9 Hz, C₃-H), 3.15–3.33 (8H, m, 4 × CH₂CH₂CH₂CH₃), 4.15 (1H, dd, *J* = 2.4, 4.6 Hz, C₄-H), 4.51–5.26 (8H, m, CHOCO, Z-OCH and 3 × PhCH₂), 7.30 (15H, s, 3 × C₆H₅).

(3S,4S)-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%). ¹H-NMR (CDCl₃) δ: 0.99 (12H, t, 4 × (CH₂)₃CH₃), 1.26–1.78 (22H, m, 2 × Me and 4 × CH₂CH₂CH₂CH₃), 2.90–2.97 (1H, m, C₃-H), 3.17–3.34 (8H, m, 4 × CH₂CH₂CH₂CH₃), 4.06–4.19 (2H, m, C₄-H and HO–CH), 4.45 (2H, d, *J* = 5.7 Hz, NCH₂), 5.26–5.39 (1H, m, CHOCO), 5.89 (1H, br s, NH), 7.09–7.35 (2H, m, C₂-H and C₅-H of the pyridine ring), 7.57–7.74 (1H, m, C₄-H of the pyridine ring), 8.48 (1H, d, *J* = 5.1 Hz, C₆-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%), [α]_D²⁰ –7.2° (*c* = 1.03, H₂O). IR (KBr): 3430, 2970, 1750, 1710, 1630, 1510, 1250 cm⁻¹. ¹H-NMR (CD₃OD) δ: 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, C₃-H), 4.01–4.07 (2H, m, C₄-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, C₅-H of the pyridine ring), 8.26 (1H, d, *J* = 7.9 Hz, C₃-H of the pyridine ring), 8.50 (1H, t, *J* = 7.9 Hz, C₄-H of the pyridine ring), 8.84 (1H, d, *J* = 5.9 Hz, C₆-H of the pyridine ring). MS (SIMS) *m/z*: 388 (M + H)⁺, 386 (M – H)[–], 372 (M – Me)[–]. *Anal.* Calcd for C₁₅H₂₁N₃O₇·S·H₂O: C, 44.43; H, 5.72; N, 10.36. Found: C, 44.49; H, 5.34; N, 10.14.

Potassium (3S,4S)-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-H₂O and chromatographed on an anion exchange resin[AG 50W-X2(K⁺ form)]. Elution of the column with H₂O and lyophilization of the combined eluate gave **9a** as a white powder (70 mg, 91%). $[\alpha]_D^{20} - 32.2^\circ$ ($c = 1.01$, H₂O). IR (KBr): 3450, 1760, 1690, 1250 cm⁻¹. ¹H-NMR (CD₃OD) δ : 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, C₃-H), 4.01–4.18 (1H, m, HO-CH), 4.14 (1H, dd, $J = 2.6, 4.4$ Hz, C₄-H), 5.09–5.24 (1H, m, CHOCO). MS (SIMS) m/z : 281 (M-K)⁺. Anal. Calcd for C₈H₁₃KN₂O₇S·1.5H₂O: 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 (3S,4S)-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%), $[\alpha]_D^{20} - 20.6^\circ$ ($c = 1.49$, H₂O). IR (KBr): 3430, 3000, 1760, 1710, 1530, 1260, 1040 cm⁻¹. ¹H-NMR (CD₃OD) δ : 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, C₃-H), 4.01–4.19 (2H, m, C₄-H and HO-CH), 5.05–5.32 (1H, m, CHOCO). MS (SIMS) m/z : 335 (M+H)⁺, 373 (M+K)⁺. Anal. Calcd for C₉H₁₅KN₂O₇S·H₂O: C, 30.67; H, 4.86; N, 7.95. Found: C, 30.90; H, 4.83; N, 7.93.

Potassium (3S,4S)-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%), $[\alpha]_D^{20} - 9.8^\circ$ ($c = 1.51$, H₂O). IR (KBr): 3460, 2970, 1750, 1680, 1390, 1250 cm⁻¹. ¹H-NMR (CD₃OD) δ : 1.27 (3H, d, $J = 6.4$ Hz, Me), 1.36 (3H, d, $J = 6.6$ Hz, Me), 2.91 (6H, s, Me₂N), 2.99 (1H, dd, $J = 2.6, 6.2$ Hz, C₃-H), 4.01–4.17 (2H, m, C₄-H and HO-CH), 5.12–5.25 (1H, m, CHOCO). MS (SIMS) m/z : 309 (M-K)⁺. Anal. Calcd for C₁₀H₁₇KN₂O₇S·1.5H₂O: C, 31.99; H, 5.37; N, 7.46. Found: C, 32.02; H, 5.43; N, 7.72.

Dipotassium (3S,4S)-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%), $[\alpha]_D^{20} - 31.0^\circ$ ($c = 1.21$, H₂O). IR (KBr): 3370, 1760, 1690, 1610, 1540, 1250, 1150 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ : 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, C₃-H), 3.25 (2H, d, $J = 4.6$ Hz, NCH₂COO), 3.66–3.92 (2H, m, C₄-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 C₁₀H₁₄K₂N₂O₉S·1.3H₂O: C, 27.30; H, 3.80; N, 6.37. Found: C, 27.59; H, 4.12; N, 6.50.

Dipotassium (3S,4S)-4-[(S)-1-(N-Carboxylatomethyl-N-methylcarbamoyloxy)ethyl]-3-[(R)-1-hydroxyethyl]-2-azetidinone-1-sulfonate (9e)¹³ Prepared from **15e** (0.415 g, 0.51 mmol) as a white powder (0.178 g, 83%). $[\alpha]_D^{20} - 15.7^\circ$ ($c = 1.67$, H₂O). IR (KBr): 3500, 3000, 1760, 1690, 1600, 1410, 1240 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ : 1.10 (1.5H, d, $J = 6.5$ Hz, Me), 1.12 (1.5H, d, $J = 6.5$ Hz, Me), 1.14 (1.5H, 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, C₃-H), 2.79 (1.5H, s, NMe), 2.82 (2H, brs, C₃-H and NMe), 3.69 (2H, brs, NCH₂COO), 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, C₄-H), 3.91 (0.5H, dd, $J = 2.2, 4.3$ Hz, C₄-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 (3S,4S)-3-[(R)-1-Hydroxyethyl]-4-[(S)-1-((piperazin-1-yl)-carbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (9f) Prepared from **15f** (0.726 g, 0.84 mmol) as a white powder (0.285 g, 87%), $[\alpha]_D^{20} + 155^\circ$ ($c = 1.73$, H₂O). IR (KBr): 3470, 2980, 1760, 1690, 1430, 1250 cm⁻¹. ¹H-NMR (CD₃OD) δ : 1.27 (3H, d, $J = 6.4$ Hz, Me), 1.36 (3H, d, $J = 6.5$ Hz, Me), 2.82 (4H, brs, CH₂NHCH₂), 2.94 (1H, dd, $J = 2.6, 6.6$ Hz, C₃-H), 3.48–3.63 (4H, m, CH₂N(CO)CH₂), 4.05 (1H, dq, $J = 6.4, 6.6$ Hz, HO-CH), 4.12 (1H, dd, $J = 2.6, 5.5$ Hz, C₄-H), 5.17 (1H, dq, $J = 5.5, 6.5$ Hz, CHOCO). MS (SIMS) m/z : 390 (M+H)⁺, 428 (M+K)⁺.

Potassium (3S,4S)-3-[(R)-1-Hydroxyethyl]-4-[(S)-1-(N-(pyridin-2-yl-methyl)carbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (9g) Prepared from **15g** (0.322 g, 0.43 mmol) as a white powder (0.159 g, 90%), $[\alpha]_D^{20} - 42.8^\circ$ ($c = 1.65$, H₂O). IR (KBr): 3400, 1760, 1710, 1540, 1260 cm⁻¹. ¹H-NMR (CD₃OD) δ : 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, C₃-H), 4.08 (1H, dq, $J = 6.2, 6.3$ Hz, HO-CH), 4.16 (1H, dd, $J = 2.4, 5.0$ Hz, C₄-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, C₅-H of the pyridine ring), 7.47 (1H, d, $J = 7.7$ Hz, C₃-H of the pyridine ring), 7.81 (1H, ddd, $J = 1.7, 7.7, 7.7$ Hz, C₄-H of the pyridine ring), 8.45 (1H, d, $J = 5.0$ Hz, C₆-H of the pyridine ring). MS (SIMS) m/z : 455 (M+K)⁺. Anal. Calcd for C₁₄H₁₈KN₃O₇S·0.25H₂O: C, 40.42; H, 4.48; N, 10.10. Found: C, 40.40; H, 4.50; N, 9.87.

Potassium (3S,4S)-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%), $[\alpha]_D^{20} - 19.3^\circ$ ($c = 1.63$, H₂O). IR (KBr): 3400, 1760, 1710, 1540, 1260 cm⁻¹. ¹H-NMR (CD₃OD) δ : 0.40–0.70 (4H, m, CH₂CH₂), 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, C₃-H), 3.98–4.30 (2H, m, C₄-H and CHOCO), 5.06–5.24 (1H, m, HO-CH). MS (SIMS) m/z : 361 (M+H)⁺, 399 (M+K)⁺. Anal. Calcd for C₁₁H₁₇KN₂O₇S·H₂O: C, 34.91; H, 5.06; N, 7.40. Found: C, 34.97; H, 5.11; N, 7.40.

Potassium (3S,4S)-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%), $[\alpha]_D^{20} - 19.2^\circ$ ($c = 1.20$, H₂O). IR (KBr): 3420, 2980, 1760, 1710, 1530, 1260 cm⁻¹. ¹H-NMR (CD₃OD-D₂O) δ : 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, C₃-H), 3.20–3.30 (2H, m, NCH₂-CH₂O), 3.56–3.65 (2H, m, NCH₂CH₂O), 4.12 (1H, dq, $J = 5.8, 6.4$ Hz, HO-CH), 4.16 (1H, dd, $J = 2.5, 5.2$, C₄-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 C₁₀H₁₇KN₂O₈S·0.5H₂O: C, 32.16; H, 4.86; N, 7.50. Found: C, 31.97; H, 4.88; N, 7.56.

Potassium (3S,4S)-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%), $[\alpha]_D^{20} - 25.4^\circ$ ($c = 1.22$, H₂O). IR (KBr): 3450, 3370, 1760, 1710, 1610, 1530, 1450, 1235 cm⁻¹. ¹H-NMR (CD₃OD) δ : 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, C₃-H), 4.08 (1H, dq, $J =$ each 6.4 Hz, HO-CH), 4.20 (1H, dd, $J = 2.6, 4.9$ Hz, C₄-H), 5.26 (1H, dq, $J = 4.9, 6.4$ Hz, CHOCO), 7.00 (1H, t, $J = 7.4$ Hz, C₄-H of the benzene ring), 7.26 (2H, dd, $J = 7.4, 7.9$ Hz, C₃-H and C₅-H of the benzene ring), 7.41 (2H, d, $J = 7.9$ Hz, C₂-H and C₆-H of the benzene ring). MS (SIMS) m/z : 435 (M+K)⁺. Anal. Calcd for C₁₄H₁₇KN₂O₇S·0.25H₂O: C, 41.93; H, 4.40; N, 6.99. Found: C, 41.78; H, 4.18; N, 6.93.

Potassium (3S,4S)-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%), $[\alpha]_D^{20} - 26.6^\circ$ ($c = 1.62$, H₂O). IR (KBr): 3450, 3360, 1755, 1610, 1535, 1230 cm⁻¹. ¹H-NMR (CD₃OD) δ : 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, C₃-H), 4.07 (1H, dq, $J =$ each 6.4 Hz, HO-CH), 4.19 (1H, dd, $J = 2.6, 5.0$ Hz, C₄-H), 5.24 (1H, dq, $J = 5.0, 6.4$ Hz, CHOCO), 6.96–7.02 (2H, m, C₃-H and C₅-H of the benzene ring), 7.39–7.43 (2H, m, C₂-H and C₆-H of the benzene ring). MS (SIMS) m/z : 453 (M+K)⁺. Anal. Calcd for C₁₄H₁₆FKN₂O₇S: C, 40.57; H, 3.89; N, 6.76. Found: C, 40.42; H, 3.69; N, 6.84.

Dipotassium (3S,4S)-3-[(R)-1-Hydroxyethyl]-4-[(S)-1-(N-methoxy-N-sulfonatocarbamoyloxy)ethyl]-2-azetidinone-1-sulfonate (9l) and Potassium (3S,4S)-3-[(R)-1-Hydroxyethyl]-4-[(S)-1-(N-methoxy-N-sulfonatocarbamoyloxy)ethyl]-2-azetidinone (18) A mixture of **14l** (0.110 g, 0.35 mmol) and SO₃-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 KH₂PO₄ (15 ml) were added, and the mixture was extracted with CH₂Cl₂. The dichloromethane extracts were combined and dried over anhydrous MgSO₄. Filtration and concentration *in vacuo* gave an oily residue which was separated by column chromatography (SiO₂, 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**: $[\alpha]_D^{20} + 1.3^\circ$ ($c = 1.35$, H₂O). IR (KBr): 3500, 2980, 2940, 1760, 1250 cm⁻¹. ¹H-NMR (CD₃OD) δ : 1.38 (3H, d, $J = 6.4$ Hz, Me), 1.44 (3H, d, $J = 6.4$ Hz, Me), 3.22 (1H, dd, $J = 2.7, 6.0$ Hz, C₃-H), 3.66 (3H, s, OMe), 4.27 (1H, dd, $J = 2.7, 5.1$ Hz, C₄-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 C₉H₁₄K₂N₂O₁₁S·0.75H₂O: 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. ¹H-NMR (CD₃OD) δ : 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, C₃-H), 3.66 (3H, s, OMe), 3.80 (1H, dd, $J = 2.2, 6.4$ Hz, C₄-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 (3S,4S)-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%), $[\alpha]_D^{20} - 4.7^\circ$