Enantioselective synthesis of 2-isocephem and 2-isooxacephem antibiotics

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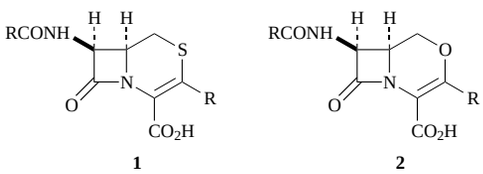
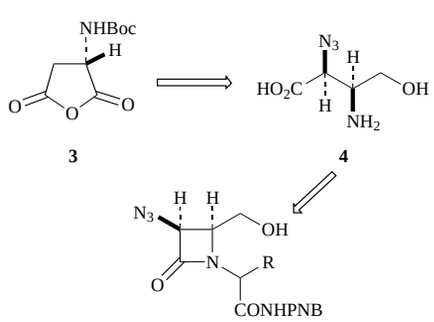
The azido lactone 8 was prepared in a highly stereoselective manner by introduction of an azide function to the lactone 6 derived from L-aspartic acid, and then was converted into (2*S*,3*S*)-3-amino-2-azido-4-hydroxybutanoic acid 4. Four-component condensation of the amino acid 4, *p*-nitrobenzyl isocyanide and formaldehyde or 2,2-diethoxyacetaldehyde furnished the corresponding 3,4-*cis*-azetidinone 16 or 26 in excellent yield. 3-Methoxy-2-isooxacephalosporin was prepared by the intramolecular acylation of imidazolide 23 derived from compound 16. 3-Unsubstituted 2-isocephem and 2-isooxacephem analogues were prepared from the azetidinone 26.

Introduction

Synthesis of the nuclear analogues of β-lactam antibiotics has attracted considerable interest. A wide range of structure types have been made available by total synthesis, and led to testing for antibacterial activity. 2-Isocephalosporin **1** and 2-isooxacephalosporin **2** have been shown to have potent antibacterial activity in their derivatives bearing hydrogen, methyl, and substituted methyl as the C-3 substituents.[1] Although one of the enantiomers exhibits superior activity as is the case with all β-lactam antibiotics, many previous syntheses led to racemic mixtures.[2] Several efforts have been directed to the synthesis of the enantiomerically pure forms. The primary problem is the construction of the *cis*-oriented chiral centres at the azetidinone ring. The existing methods for the syntheses of these compounds involve an asymmetric ketene–imine cycloaddition reaction as a key step in which a chiral auxiliary was incorporated in either imine or ketene form.[1a,1b,3,4] Our solution of this problem is to use L-aspartic acid as a chiral starting material (Scheme 1). We expected that the β-amino acid **4** having the desired two contiguous chiral centres could be derived *via* introduction of an azide group to the amino lactone **3**, which was readily available from L-aspartic acid. Subsequent four-component condensation on the amino acid can provide (3*S*,4*S*)-azetidinones having the functionality suitable to build up the fused 6-membered heterocyclic ring. In this paper we report the details of the enantioselective syntheses of 2-isocephem and 2-isooxacephems.[5]



1 **2**

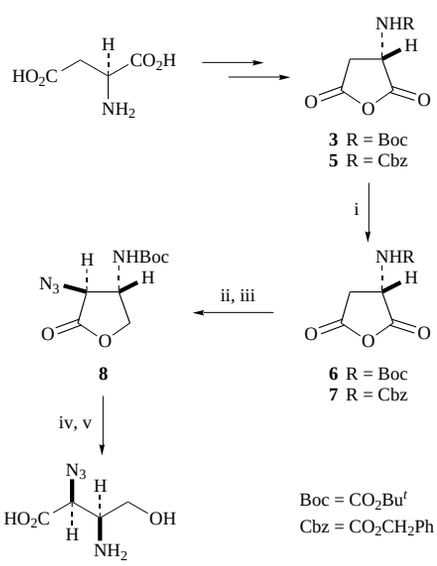


Scheme 1

Results and discussion

Synthesis of (2*S*,3*S*)-3-amino-2-azido-4-hydroxybutanoic acid

The (*S*)-lactones **6** and **7** were prepared by the reduction of N-protected L-aspartic anhydrides **3** and **5** with $NaBH_4$ in good yields (Scheme 2).[6] Treatment of compound **6** with 2 mol equiv. of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −67 °C followed by toluene-*p*-sulfonyl azide gave the desired *trans* azide lactone **8** in 50% yield. Stereochemistry of compound **8** was established on the basis of the observed coupling constant ($J_{2,3}$ 7.9 Hz) and no observation of a nuclear Overhauser enhancement (NOE) between H-2 and H-3 in the ^1H NMR spectrum. Although alkylation of the lactone **7** has been



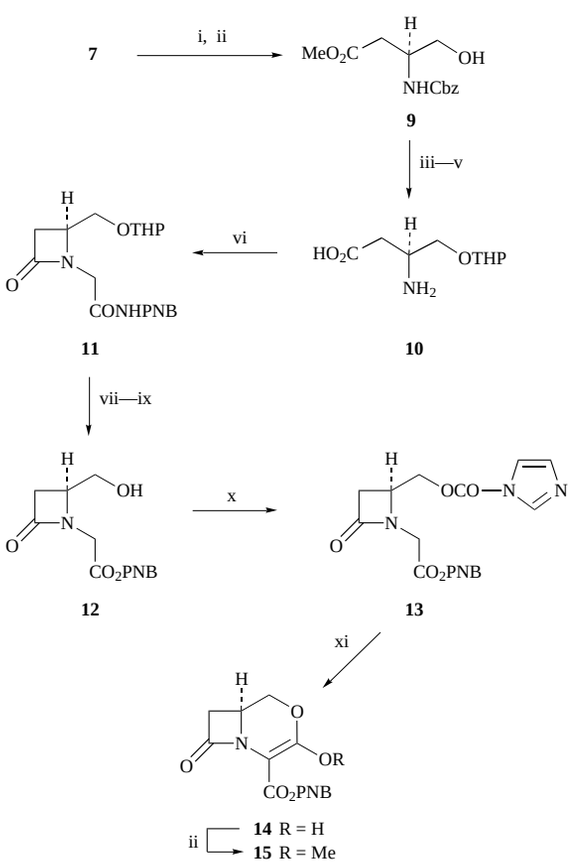
Scheme 2 *Reagents and conditions:* i, $NaBH_4$, THF; ii, LDA, THF; iii, TsN_3; iv, TFA; v, Amberlite IRA-45

reported to be accompanied by significant amounts of the *cis* isomer beside the *trans* isomer,[7] the introduction of the azide group to lactone **6** proceeded in a highly stereoselective fashion and the formation of the *cis* azide was not detected. Attempted hydrolysis of the lactone ring of compound **8** with aqueous alkali failed and led to the elimination of *tert*-butoxyformamide. However, opening of the lactone ring occurred simultaneously when the C-3 amino-protecting group was removed. Thus, deprotection of **8** with trifluoroacetic acid (TFA) and successive neutralization of the resulting trifluoroacetate with Amberlite IRA-45 in aq. methanol gave the crystalline amino acid **4** in 76% yield.

Synthesis of 3-methoxy-2-isooxacephalosporin

There are few reports concerning the synthesis of 3-heterosubstituted 2-isooxacephalosporins, although their biological activity is interesting because the corresponding 3-methoxycephalosporins show potent activity.[8] Previously we described how 3-hydroxycarbacephem and 2-oxocarbapenem ring systems could be prepared *via* an intermolecular acylation reaction as a key step.[9] This methodology was evaluated for our present purposes.

A model experiment for the construction of the 3-methoxy-2-iso-oxacephem ring system was examined with the O-protected amino acid **10** (Scheme 3). The amino acid was prepared from

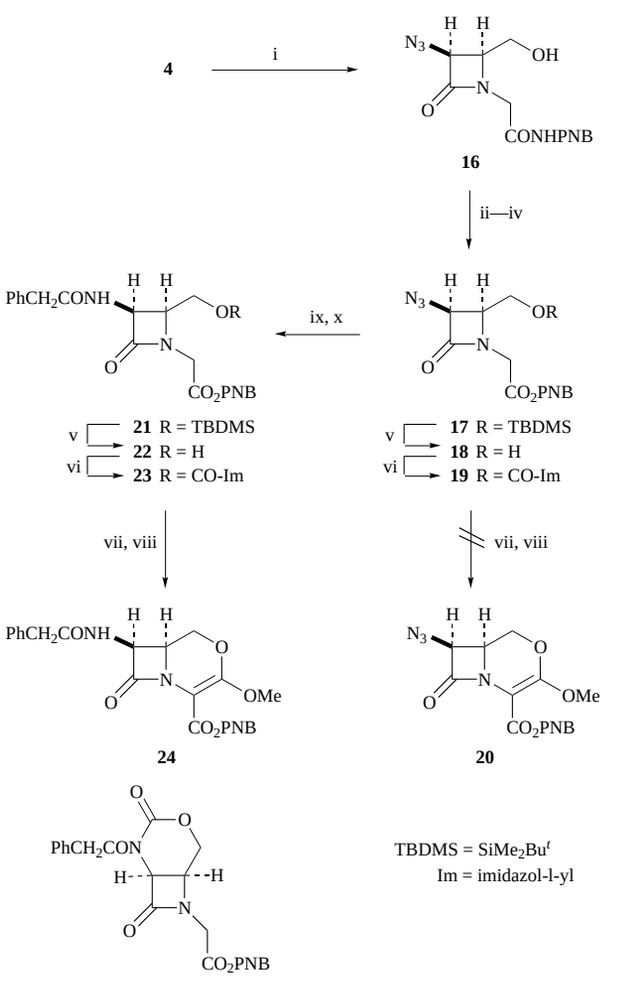


Scheme 3 *Reagents and conditions:* i, K_2CO_3; ii, CH_2N_2; iii, 2,3-dihydropyran, TsOH; iv, KOH; v, Pd–C, H_2; vi, HCHO, CNPNB, MeOH; vii, N_2O_4; viii, $ClCH_2CH_2Cl$, reflux; ix, $HClO_4$, aq. 1,4-dioxane; x, CDI; xi, LHDMS, THF, −78 °C. CNPNB = *p*-nitrobenzyl isocyanide, CDI = 1,1′-carbonyldiimidazole, LHDMS = lithium hexamethyldisilazide

the (3*S*)-lactone **7** in 85% overall yield *via* straightforward sequences consisting of hydrolysis with K_2CO_3, esterification with diazomethane, protection of the resulting hydroxy group, and removal of the other protective groups by alkali hydrolysis and hydrogenolysis. When a four-component condensation of amino acid **10**, formaldehyde and *p*-nitrobenzyl isocyanide (CNPNB) was carried out in a very dilute methanol solution at room temperature for 12 h, the azetidinone **11** was obtained in 78% yield. The *p*-nitrobenzylamide entity was then converted into the *p*-nitrobenzyl ester *via* N-nitrosation and a thermal rearrangement in refluxing CCl_4. Subsequent acid treatment gave the *p*-nitrobenzyl ester **12**.

Intramolecular acylation of various carbamate derivatives of alcohol **12** was next investigated. When the phenylthiocarbamate of alcohol **12** was subjected to intramolecular acylation by means of the procedure analogous to that reported,[9] only a low yield (10% or less) of compound **15** was obtained. In addition, attempted intramolecular acylation of the other carbamates, including the chlorocarbamate and phenoxycarbamate of alcohol **12**, resulted in no formation of bicycle **15**. The best results were accomplished with the *N*-imidazolylcarbonyl entity as a carbamoyl group. Compound **12** was treated with 1,1′-carbonyldiimidazole (CDI) to give the carbamate **13** in 87% yield. Treatment of imidazolecarboxylate **13** with 2 mol equiv. of lithium hexamethyldisilazide (LHMDS) in THF at −78 °C for 3 min and successive quenching with acetic acid produced the crude 3-hydroxy-2-isooxacephem **14**. Compound **14** was labile and hence was treated without purification with an excess of diazomethane to give the desired 3-methoxy-2-isooxacephem **15** in 64% yield from azetidinone **13**. Thus, an efficient method for the construction of the 3-methoxy-2-iso-oxacephem ring system was established.

The (2*S*,3*S*)-azido amino acid **4** was next subjected to the four-component condensation with formaldehyde and CNPNB to give the (3*S*,4*S*)-azidoazetidinone **16** in 96% yield (Scheme 4).

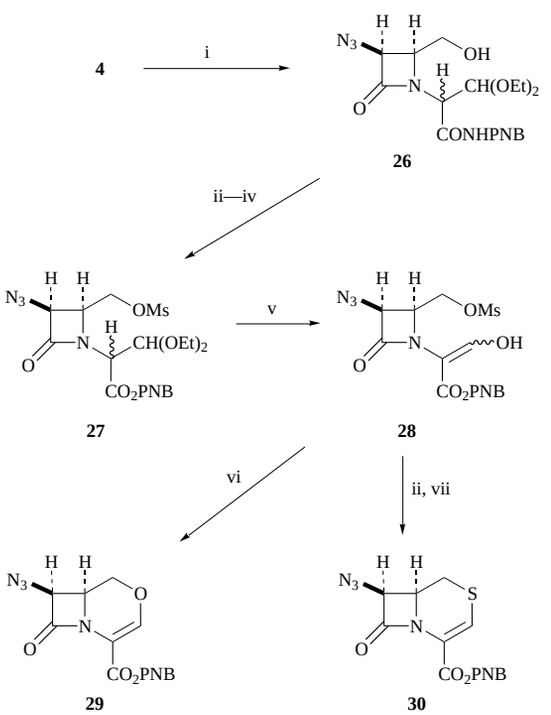


Scheme 4 *Reagents and conditions:* i, HCHO, CNPNB, MeOH; ii, TBDMSCl; iii, N_2O_4; iv, $ClCH_2CH_2Cl$, reflux; v, HCl; vi, CDI; vii, LHMDS, −78 °C; viii, CH_2N_2; ix, H_2S, Et_3N; x, $PhCH_2COCl$

The *cis*-orientation of the C-3 and C-4 hydrogens of compound **16** was confirmed by the observed coupling constant ($J_{3,4}$ 5.1 Hz) in the ^{1}H NMR spectrum. After the hydroxy group of compound **16** was protected with *tert*-butyldimethylsilyl chloride (TBDMSCl), the *p*-nitrobenzylamide was transformed *via* N-nitrosation with N_2O_4 into the *p*-nitrobenzyl ester. Removal of the TBDMS group with aq. HCl gave alcohol **18** in 90% yield which was converted upon treatment with CDI into the carbamate **19** in 71% yield. However, attempted cyclization of **19** with LHDMS led to the formation of a complex mixture and not the expected 3-methoxy-2-isooxacephalosporin **20**. Therefore, we examined prior to cyclization, conversion of the azide group of compound **17** into an amide because the formation of amide anion would be expected to retard the formation of a carbanion at C-3 during the cyclization process. Reduction of the azide group with H_2S in the presence of triethylamine and subsequent acylation with phenylacetyl chloride afforded compound **21** in 75% yield, which was then converted into the carbamate **23** in 84% yield. Cyclization of the carbamate **23** in a manner similar to that described for compound **15** gave the 3-methoxy-2-isooxacephalosporin **24** in 53% yield without epimerization at the 3 position. In addition, unfavourable cyclization between the nitrogen and the carbamate leading to bicycle **25** was not observed.

Synthesis of 2-isocephem and 2-iso-oxacephem nuclei

An azetidinone suitable for the construction of 3-unsubstituted 2-isocephem and 2-isooxacephem targets could be also prepared from the amino acid **4** by a four-component condensation (Scheme 5). When an equimolar mixture of the amino



Scheme 5 *Reagents and conditions:* i, $(EtO)_2CHCHO$, CNPNB, MeOH; ii, MsCl, Et_3N; iii, N_2O_4, AcONa; iv, CCl_4, reflux; v, TFA; vi, Et_3N; vii, H_2S, Et_3N

acid **4**, 2,2-diethoxyacetaldehyde and CNPNB was stirred in methanol at room temperature, the *cis*-azetidinone **26** was obtained as a 1:1 mixture of the diastereomers at the C-1′ position in 93% yield.

Methanesulfonylation of the hydroxy group of compound **26** followed by conversion of the amide group into an ester *via* N-nitrosation gave compound **27** in 57% yield, which corresponded to the key intermediate in the synthesis of 2-isocephem and 2-isooxacephem systems reported by Doyle *et al.*[2a] Finally, according to Doyle's procedure, compound **27** was converted into the 7-azido-2-isooxacephem **29** by hydrolysis (TFA) followed by treatment of the resulting vinyl alcoholic intermediate **28** with triethylamine. Alternatively, methanesulfonylation of intermediate **28** and subsequent treatment with hydrogen sulfide furnished the 7-azido-2-isocephem **30**.

Conclusions

We have developed a convenient method for the preparation of 2-isocephem and 2-isooxacephem in an enantioselective fashion. The strategy involves the four-component condensation of (2*S*,3*S*)-amino acid **4** leading to the excellent formation of (3*S*,4*S*)-azetidinones **16** and **26**. Intramolecular acylation of imidazolecarboxylate **23** derived from azide **16** gave the 3-methoxy-2-isooxacephalosporin **24**. 3-Unsubstituted 2-isocephem **30** and 2-isooxacephem **29** were prepared from the azetidinone **26** using the reported procedure.

Experimental

All mps were measured on a Gallenkamp micro melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrometer. UV spectra were recorded on a Hitachi U-3210 spectrometer. ^{1}H NMR spectra were measured at 270 MHz on a JEOL 270EX spectrometer or at 360 MHz on a Bruker AM-360 spectrometer, using $SiMe_4$ as the internal standard. *J*-Values are given in Hz. ^{13}C NMR spectra were recorded at 68 MHz on a JEOL 270EX spectrometer or at 90 MHz on a Bruker AM-260 spectrometer. Solvent peak ($CDCl_3$: δ_C 77.0) was used for the internal standard. Mass spectra were recorded on a Hitachi M-80B spectrometer. Optical rotations were measured on a Perkin-Elmer 240c polarimeter and $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Column chromatography was carried out on silica gel. Extracts were dried over $MgSO_4$ and evaporated under reduced pressure.

(3*S*)-3-(*tert*-Butoxycarbonylamino)-4-butanolide 6

The procedure reported for the preparation of compound **7**[6] was modified as follows. To a well stirred suspension of $NaBH_4$ (12.4 g, 0.328 mol) in THF (100 cm^3) was added a solution of L-*N*-(*tert*-butoxycarbonyl)aspartic acid anhydride **3** (70 g, 0.325 mol) in THF (350 cm^3) at 0 °C over a period of 1.5 h. After being stirred for an additional 2 h, the mixture was treated carefully with 6 M aq. hydrochloric acid (90 cm^3), and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried and evaporated. The remaining oil was dissolved in benzene (500 cm^3) and the solution was heated under reflux using a Dean–Stark apparatus for 3 h. The benzene solution was washed with saturated aq. $NaHCO_3$, dried and evaporated. The resulting solid was recrystallized from ethyl acetate–hexane to give *title compound* **6** as crystals (50 g, 76%), mp 108 °C (Found: C, 53.47; H, 7.23; N, 6.96. $C_9H_{15}NO_4$ requires C, 53.70; H, 7.52; N, 6.96%); $[\alpha]_D^{25}$ −61 (*c* 1.0, EtOH); ν_{max}(KBr)/cm^{-1} 1770 and 1680; δ_H(270 MHz; $CDCl_3$) 1.45 (9 H, s, CMe_3), 2.47 (1 H, dd, *J* 3.6 and 17.8, 2-H), 2.84 (1 H, dd, *J* 7.9 and 17.8, 2-H), 4.22 (1 H, d, *J* 6.0, 4-H), 4.47–4.53 (2 H, m, 3- and 4-H) and 5.24 (1 H, br s, NH); δ_C(68 MHz; $CDCl_3$) 28.2, 34.8, 47.6, 73.7, 80.3, 155.1 and 157.3.

(2*S*,3*S*)-2-Azido-3-(*tert*-butoxycarbonylamino)-4-butanolide 8

A solution of compound **6** (5 g, 24.9 mmol) in THF (30 cm^3) was added at −78 °C to a solution of LDA prepared from diisopropylamine (7.35 cm^3, 52.5 mmol) and 1.5 M butyllithium–hexane solution (35 cm^3, 52.5 mmol). The mixture was stirred for 2 h at −78 °C and treated with a solution of toluene-*p*-sulfonyl azide (5.9 g, 30 mmol) in THF (30 cm^3). After being stirred for 1 h at −78 °C, the mixture was treated with trimethylsilyl chloride (9.5 mg, 75 mmol), warmed to 0 °C over a period of 1 h and then concentrated. The remaining residue was shaken with ice–water (100 cm^3) and ethyl acetate (100 cm^3). The organic layer was dried and evaporated. Column chroma-

tography (benzene–ethyl acetate, 14:1, v/v) of the residue gave title compound **8** as crystals (3 g, 50%), mp 110–111 °C (from diisopropyl ether) (Found: C, 44.65; H, 5.76; N, 23.40. $C_9H_{14}N_4O_4$ requires C, 44.63; H, 5.82; N, 23.14%); $[\alpha]_D^{25}$ −69 (*c* 1.0, EtOH); ν_{max}(KBr)/cm^{-1} 2100, 1780 and 1680; δ_H(360 MHz; $CDCl_3$) 1.46 (9 H, s, CMe_3), 4.08–4.14 (4 H, m, OH, NH_2 and 4-H), 4.15 (1 H, br d, *J* 7.9, 2-H), 4.45 (1 H, br s, 3-H), 4.55 (1 H, dd, *J* 7.4 and 7.4, 4-H) and 4.94 (1 H, br s, NH); δ_C(67.8 MHz) 28.2, 53.1, 60.4, 68.7, 81.1, 154.9 and 171.4.

(2*S*,3*S*)-3-Amino-2-azido-4-hydroxybutanoic acid 4

Compound **8** (5 g, 20.7 mmol) was treated with TFA (10 cm^3) and anisole (2 cm^3) at 0 °C for 30 min. The mixture was condensed to remove the TFA and the residue was taken into water (50 cm^3). The solution was washed with diethyl ether, adjusted to pH 6.0 with Amberlite IRA-45, and stirred for 6 h while the pH was kept at 6.0 by addition of Amberlite IRA-45. After filtration, the filtrate was evaporated to give compound **4** as crystals (2.5 g, 76%), mp 135–137 °C (from aq. acetone) (Found: C, 30.23; H, 4.98; N, 35.03. $C_4H_8N_4O_3$ requires C, 30.00; H, 5.03; N, 34.99%); $[\alpha]_D^{25}$ −149 (*c* 1.0, water); δ_H[270 MHz; CD_3OD–$(CD_3)_2SO$] 3.45 (1 H, ddd, *J* 5.0, 5.0 and 7.6, 3-H), 3.63 (1 H, dd, *J* 7.6 and 11.5, 4-H), 3.76 (1 H, dd, *J* 5.0 and 11.5, 4-H) and 4.14 (1 H, d, *J* 5.0, 2-H); δ_C[67.8 MHz; CD_3OD–$(CD_3)_2SO$] 54.9, 60.5, 62.9 and 172.8.

Methyl 3-(*N*-benzyloxycarbonylamino)-4-hydroxybutanoate 9

A solution of compound **7** (10 g, 42.5 mmol) in 50% aq. acetone (100 cm^3) containing K_2CO_3 (7 g, 50 mmol) was heated at 50 °C for 3 h. The cooled mixture was adjusted to pH 2.0 with hydrochloric acid and extracted with ethyl acetate. The extract was treated with an excess of diazomethane–diethyl ether solution. The mixture was treated with several drops of AcOH, washed successively with aq. $NaHCO_3$ and brine, dried and evaporated to give ester **9** as an oil (11 g), which was used in the next step without further purification; ν_{max}(neat)/cm^{-1} 3400, 2950, 1730, 1710 and 1690; δ_H(270 MHz; $CDCl_3$) 2.60 (2 H, br d, *J* 6.3, 2-H_2), 3.23 (1 H, t, *J* 5.6, OH), 3.63 (3 H, s, OMe), 3.65 (2 H, m, 4-H_2), 4.05 (1 H, m, 3-H), 5.05 (2 H, s, CH_2Ph), 5.70 (1 H, d, *J* 8.2, NH) and 7.32 (5 H, br s, Ph); δ_C(67.8 MHz; $CDCl_3$) 35.5, 49.7, 51.7, 63.8, 66.7, 127.96, 128.03, 128.4, 136.2, 156.2 and 172.1; *m*/*z* 267 (M^+).

(3*S*)-3-Amino-4-(tetrahydropyran-2-yloxy)butyric acid 10

Compound **9** (11.4 g, 42.7 mmol) was treated with 2,3-dihydropyran (4.7 cm^3, 51.6 mmol) and toluene-*p*-sulfonic acid hydrate (TsOH) (0.08 g, 0.42 mmol) in CH_2Cl_2 (50 cm^3) for 1 h at room temperature. The mixture was washed successively with aq. $NaHCO_3$ and brine, dried and evaporated. The remaining oil was dissolved in methanol (50 cm^3) and 2 M aq. KOH (20 cm^3) was added dropwise. The mixture was stirred overnight at room temperature and evaporated. The residue was taken into water (30 cm^3) and the aqueous solution was washed with diethyl ether, adjusted to pH 2.0, and extracted with ethyl acetate. The oily residue was dissolved in EtOH (130 cm^3) and hydrogenated at room temperature under atmospheric pressure in the presence of 5% Pd–C (1.3 g). The oily product was triturated in acetone to give *title amino acid* **10** (7.5 g, 85%) as crystals, mp 158–160 °C (from aq. acetone) (Found: C, 50.18; H, 9.01; N, 7.28. $C_8H_{17}NO_4$ requires C, 50.25; H, 8.96; N, 7.32%); $[\alpha]_D^{25}$ −31 (*c* 1.0, MeOH); δ_H[270 MHz; CD_3OD–$(CD_3)_2SO$] 1.51–1.85 (6 H, m, $CH_2CH_2CH_2$), 2.40 (2 H, m, 2-H_2), 3.25–3.61 (3 H, m, 3-H and OCH_2CH$_2$), 3.73–3.88 (2 H, m, 4-H_2) and 4.62 (1 H, m, OCHO); δ_C[67.8 MHz; CD_3OD–$(CD_3)_2SO$] 20.4, 20.5, 26.4, 31.4, 36.71, 36.75, 50.4, 50.5, 63.3, 63.4, 68.1, 68.6, 100.1, 100.7 and 176.7.

(4*S*)-1-(*p*-Nitrobenzylcarbamoylmethyl)-4-(tetrahydropyran-2-yloxymethyl)azetidin-2-one 11

A solution of amino acid **10** (4.0 g, 19.7 mmol), CNPNB (3.3 g, 20.4 mmol) and 35% aq. formaldehyde (1.8 g, 21.7 mmol) in methanol (400 cm^3) was stirred at room temperature for 12 h. The methanol was evaporated off and the residue was dissolved in ethyl acetate. The solution was washed successively with aq. $NaHCO_3$ and brine, dried and evaporated to give *title azetidinone* **11** as an oil (5.8 g, 78%), ν_{max}(CH_2Cl_2)/cm^{-1} 1760, 1680 and 1520; *m*/*z* (FAB) 378 (M^+ + 1).

***p*-Nitrobenzyl (2*S*)-2-hydroxymethyl-4-oxoazetidine-1-acetate 12**

A solution of amide **11** (4.6 g, 12.2 mmol) in $CHCl_3$ (50 cm^3) was added dropwise to a suspension of N_2O_4 (37.4 mmol) and sodium acetate (4.1 g, 50 mmol) in $CHCl_3$ (20 cm^3) at 0 °C and the mixture was then stirred for 1 h at 0 °C. Saturated aq. $NaHCO_3$ (9 cm^3) was added and the organic layer was dried and evaporated. The residue was heated in refluxing 1,2-dichloroethane (100 cm^3) for 3 h. After evaporation of the mixture, column chromatography of the residue gave an oil (3.0 g, 64%). The oil (2.9 g, 7.67 mmol) was dissolved in 1,4-dioxane (24 cm^3) and treated with 20% aq. $HClO_4$ (8 ml) at 0 °C. The solution was stirred for 30 min at 0 °C, poured into aq. $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated to give *title ester* **12** as crystals (2.2 g, 98%), mp 117–118 °C (from benzene–hexane) (Found: C, 52.98; H, 4.89; N, 9.47. $C_{13}H_{14}N_2O_6$ requires C, 53.06; H, 4.80; N, 9.52%); ν_{max}(CH_2Cl_2)/cm^{-1} 3520, 1765 and 1750; δ_H(360 MHz; $CDCl_3$) 2.98 (1 H, dd, *J* 4.8 and 14.6, 3-H), 3.04 (1 H, dd, *J* 2.7 and 14.6, 3-H), 3.24 (1 H, m, 2-C*H*HOH), 3.67 (1 H, m, 2-H), 3.86 (2 H, m, 2-CH*HOH*), 3.86 and 4.47 (2 H, ABq, *J* 18.4, NCH_2CO_2), 5.29 (2 H, s, CH_2Ar), 7.53 (2 H, d, *J* 8.7, ArH) and 8.25 (2 H, d, *J* 8.7, ArH); δ_C(90 MHz; $CDCl_3$) 38.6, 42.4, 54.6, 61.4, 66.0, 123.8, 128.6, 141.8, 147.9, 167.6 and 169.9.

***p*-Nitrobenzyl (2*S*)-2-(imidazol-1-ylcarbonyloxymethyl)-4-oxoazetidine-1-acetate 13**

A solution of the alcohol **12** (0.2 g, 0.68 mmol) and CDI (0.12 g, 0.75 mmol) in CH_2Cl_2 (5 cm^3) was stirred at room temperature overnight. The mixture was washed successively with aq. $NaHCO_3$ and brine, dried and evaporated to give *title diester* **13** as an oil (0.226 g, 87%), ν_{max}(CH_2Cl_2)/cm^{-1} 1770 and 1750; δ_H(270 MHz; $CDCl_3$) 2.29 (1 H, dd, *J* 3.0 and 15.0, 3-H), 3.25 (1 H, dd, *J* 5.4 and 15.0, 3-H), 4.07 and 4.23 (2 H, ABq, *J* 18.0, NCH_2CO_2), 4.22 (1 H, m, 2-H), 4.48 (1 H, dd, *J* 6.4 and 11.8, 2-C*H*HO), 4.80 (1 H, dd, *J* 3.0 and 11.8, 2-CH*H*O), 5.19 (2 H, s, CH_2Ar), 7.07 (1 H, br s, imidazole H), 7.37 (1 H, br s, imidazole H), 7.49 (2 H, d, *J* 8.7, ArH), 8.08 (1 H, s, imidazole H) and 8.22 (2 H, d, *J* 8.7, ArH); δ_C(67.8 MHz; $CDCl_3$) 40.0, 42.4, 50.3, 65.8, 67.6, 116.9, 123.8, 128.7, 131.0, 136.9, 148.1, 166.0 and 167.8; *m*/*z* (FAB) 389 (M^+ + 1).

***p*-Nitrobenzyl (6*S*)-3-methoxy-8-oxo-4-oxa-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylate 15**

The carbamate **13** (100 mg, 0.26 mmol) was dissolved in THF (5 cm^3) and treated at −78 °C with a 1 M LHMDS–hexane solution (0.78 cm^3). The solution was stirred for 3 min at −78 °C and then treated with AcOH (0.044 cm^3). The mixture was poured into 5% aq. citric acid (2 cm^3) and extracted with ethyl acetate. The extract of intermediate **14** was washed with water, dried and treated, while cooled in ice, with an excess of diazomethane in diethyl ether. The mixture was then set aside at room temperature for 3 h, and then evaporated. Flash chromatography of the residue on silica gel (benzene–ethyl acetate, 2:1, v/v) gave *title compound* **15** as crystals (50 mg, 58%), mp 146–147 °C (from ethyl acetate–isopropyl ether) (Found: C, 48.13; H, 4.61; N, 6.98. $C_8H_9NO_5$ requires C, 48.25; H, 4.55; N, 7.03%); $[\alpha]_D^{25}$ +188.8 (*c* 0.5, $CHCl_3$); ν_{max}(CH_2Cl_2)/cm^{-1} 1775, 1770 and 1600; δ_H(360 MHz; $CDCl_3$) 2.64 (1 H, dd, *J* 1.8 and 15.0, 7-H), 3.47 (1 H, dd, *J* 5.0 and 15.0, 7-H), 3.65 (1 H, m, 6-H), 3.90 (3 H, s, OMe), 3.99 (1 H, dd, *J* 9.7 and 10.7, 5-H), 4.86 (1 H, dd, *J* 3.7 and 10.7, 5-H), 5.22 and 5.44 (2 H, ABq, *J* 13.9, CH_2Ar), 7.64 (2 H, d, *J* 8.7, ArH) and 8.21 (2 H, d, *J* 8.7, ArH);

δ_C(67.8 MHz; $CDCl_3$) 41.0, 41.2, 55.8, 64.5, 72.6, 89.7, 123.5, 128.0, 144.0, 147.2, 159.3, 161.8 and 166.4; λ_{max}(MeOH)/nm 274 (ε/dm^3 mol^{-1} cm^{-1} 18 100).

(3*S*,4*S*)-3-Azido-4-hydroxymethyl-1-(*p*-nitrobenzylcarbamoylmethyl)azetidin-2-one 16

By means of the procedure described for the preparation of compound **11**, the amino acid **4** (0.5 g, 3.1 mmol) was treated with CNPNB (0.53 g, 3.2 mmol) and 35% aq. formaldehyde (0.28 g, 3.3 mmol) in methanol (120 cm^3) to give *title compound* **16** as crystals (1.0 g, 96%). Recrystallization from ethyl acetate–diisopropyl ether gave a pure sample, mp 91–92 °C (Found: C, 46.52; H, 4.38; N, 24.9. $C_{13}H_{14}N_6O_5$ requires C, 46.71; H, 4.22; N, 25.14%); ν_{max}(CH_2Cl_2)/cm^{-1} 2100, 1780 and 1680; δ_H[360 MHz; $(CD_3)_2SO$] 3.84 (2 H, m, 4-CH_2OH), 3.88 and 4.22 (2 H, ABq, *J* 16.8, NCH_2CO), 3.96 (1 H, m, 4-H), 4.50 (2 H, br s, CH_2Ar), 4.78 (1 H, d, *J* 5.1, 3-H), 4.91 (1 H, t, *J* 5.5, OH), 7.78 (2 H, d, *J* 8.4, ArH), 8.18 (2 H, d, *J* 8.4, ArH) and 8.66 (1 H, m, NH); δ_C[67.8 MHz; $(CD_3)_2SO$] 41.6, 43.3, 58.4, 58.5, 64.1, 122.7, 127.3, 145.3, 146.0, 164.3 and 167.3.

***p*-Nitrobenzyl (2*S*,3*S*)-3-azido-2-(*tert*-butyldimethylsiloxymethyl)-4-oxoazetidine-1-acetate 17**

A solution of amide **16** (1.0 g, 2.99 mmol), imidazole (0.5 g, 7.3 mmol) and TBDMSCl (0.45 g, 2.99 mmol) in dimethylformamide (DMF) (5 cm^3) was stirred at room temperature overnight. The mixture was poured into ice–water and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. Column chromatography of the residue gave an oil (1.2 g, 89%).

In the same manner as described for the preparation of compound **12**, the oil (1.0 g, 2.23 mmol) was treated with N_2O_4 (6.7 mmol) to give *title ester* **17** as an oil (0.67 g, 67%), ν_{max}(CH_2Cl_2)/cm^{-1} 2100, 1775 and 1750; δ_H(360 MHz; $CDCl_3$) 0.05 (6 H, s, $SiMe_2$), 0.85 (9 H, s, CMe_3), 3.84 (2 H, m, 2-CH_2O), 4.02 and 4.34 (2 H, ABq, *J* 18.0, NCH_2CO_2), 4.05 (1 H, m, 2-H), 4.80 (1 H, d, *J* 5.15, 3-H), 5.25 (2 H, s, CH_2Ar), 7.50 (2 H, d, *J* 8.7, ArH) and 8.23 (2 H, d, *J* 8.7, ArH); δ_C(67.8 MHz; $CDCl_3$) −5.7, 18.0, 25.6, 42.6, 58.1, 62.8, 65.0, 65.7, 123.8, 128.2, 128.6, 142.0, 147.8, 164.5 and 167.3; *m*/*z* (FAB) 450 ($M^+ + 1$).

***p*-Nitrobenzyl (2*S*,3*S*)-2-(*tert*-butyldimethylsiloxymethyl)-4-oxo-3-(phenylacetamido)azetidine-1-acetate 21**

Hydrogen sulfide gas was bubbled into a solution of azide **17** (1.0 g, 2.23 mmol) in CH_2Cl_2 (20 cm^3) at 0 °C for 3 min. Triethylamine (0.31 g, 2.23 mmol) was added and the mixture was stirred for 1 h at 0 °C. The mixture was poured into ice–water and the aqueous layer was extracted with CH_2Cl_2. After being dried, the organic layers were treated with pyridine (0.3 cm^3, 3.7 mmol) and phenylacetyl chloride (0.38 g, 2.46 mmol) for 30 min at room temperature. The mixture was washed with ice–water, dried and evaporated. Column chromatography of the residue gave *title compound* **21** as crystals (0.9 g, 75%), mp 98–99 °C (from benzene–hexane) (Found: C, 59.78; H, 6.22; N, 7.85. $C_{27}H_{35}N_3O_7Si$ requires C, 59.88; H, 6.46; N, 7.76); ν_{max}(CH_2Cl_2)/cm^{-1} 1770, 1750 and 1680; δ_H(360 MHz; $CDCl_3$) 0.014 (6 H, s, $SiMe_2$), 0.85 (9 H, s, CMe_3), 3.54 and 3.62 (2 H, ABq, *J* 15.5, CH_2Ar), 3.56 (1 H, dd, *J* 4.7 and 11.0, 2-C*H*HO), 3.77 and 4.64 (2 H, ABq, *J* 18.0, NCH_2CO_2), 3.81 (1 H, dd, *J* 2.4 and 11.0, 2-CH*H*O), 4.06 (1 H, m, 2-H), 5.25 (2 H, s, CH_2Ar), 5.49 (1 H, dd, *J* 5.15 and 9.0, 3-H), 6.27 (1 H, d, *J* 9.0, NH), 7.31 (5 H, m, Ph), 7.51 (2 H, d, *J* 9.0, ArH) and 8.25 (2 H, d, *J* 9.0, ArH); δ_C(67.8, MHz; $CDCl_3$) −5.7, 17.8, 25.6, 42.0, 43.3, 57.1, 58.7, 60.8, 65.6, 123.8, 127.2, 128.2, 128.5, 128.8, 128.9, 134.3, 141.9, 147.8, 167.3 and 171.1.

***p*-Nitrobenzyl (2*S*,3*S*)-2-hydroxymethyl-4-oxo-3-(phenylacetamido)azetidine-1-acetate 22**

A solution of silyl ether **21** (0.47 g, 0.87 mmol) in THF (5 cm^3) was treated with conc. hydrochloric acid (0.2 cm^3) and the mixture was stirred for 1 h at room temperature. The solution was poured into ice–water and extracted with CH_2Cl_2. The extract was washed successively with aq. $NaHCO_3$ and brine, dried and evaporated to give the *free alcohol* **22** as crystals (0.35 g, 95%), mp 149–150 °C (from ethyl acetate–diisopropyl ether) (Found: C, 58.97; H, 5.03; N, 9.78. $C_{21}H_{21}N_3O_7$ requires C, 59.01; H, 4.95; N, 9.83%); ν_{max}(CH_2Cl_2)/cm^{-1} 1770, 1740 and 1680; δ_H(360 MHz; $CDCl_3$) 3.48 (1 H, dd, *J* 11.0 and 12.7, 2-C*H*HOH), 3.58 and 3.64 (2 H, ABq, *J* 15.5, CH_2Ph), 3.72 and 4.55 (2 H, ABq, *J* 18.6, NCH_2CO_2), 3.87 (3 H, m, 2-H and 2-CH*HOH*), 5.25 and 5.30 (2 H, ABq, *J* 13.0, CH_2Ar), 5.62 (1 H, dd, *J* 5.15 and 9.5, 3-H), 6.88 (1 H, d, *J* 9.5, NH), 7.32 (5 H, m, Ph), 7.51 (2 H, d, *J* 8.7, ArH) and 8.25 (2 H, d, *J* 8.7, ArH); δ_C(67.8 MHz; $CDCl_3$) 42.1, 43.6, 57.5, 58.2, 60.3, 66.5, 124.0, 127.3, 128.86, 128.89, 129.3, 134.1, 141.2, 148.0, 168.0, 170.4 and 171.2.

***p*-Nitrobenzyl (2*S*,3*S*)-2-(imidazol-1-ylcarbonyloxymethyl)-4-oxo-3-(phenylacetamido)azetidine-1-acetate 23**

By means of the procedure described for the preparation of compound **14**, compound **22** (0.26 g, 0.6 mmol) was treated with a solution of CDI (0.12 g, 0.74 mmol) in CH_2Cl_2 (5 cm^3) to give *title diester* **23** as crystals (0.28 g, 88%), mp 153–154 °C (from ethyl acetate–diisopropyl ether) (Found: C, 57.47; H, 4.41; N, 13.38. $C_{25}H_{23}N_5O_8$ requires C, 57.58; H, 4.45; N, 13.43%); ν_{max}(CH_2Cl_2)/cm^{-1} 1770, 1760, 1750 and 1680; δ_H[360 MHz; $CDCl_3$–$(CD_3)_2SO$] 3.56 and 3.62 (2 H, ABq, *J* 14.5, CH_2Ph), 4.08 and 4.20 (2 H, ABq, *J* 18, NCH_2CO_2), 4.26 (1 H, m, 2-H), 4.48 (2 H, d, *J* 5.1, 2-CH_2O), 5.15 and 5.20 (2 H, ABq, *J* 13.0, CH_2Ar), 5.42 (1 H, dd, *J* 5.1 and 7.6, 3-H), 7.01 (1 H, br s, imidazole H), 7.26 (5 H, m, Ph), 7.35 (1 H, br s, imidazole H), 7.48 (2 H, d, *J* 8.5, ArH), 7.97 (1 H, s, imidazole H), 8.05 (1 H, d, *J* 7.6, NH) and 8.21 (2 H, d, *J* 8.5, ArH); δ_C[67.8 MHz; $CDCl_3$–$(CD_3)_2SO$] 42.0, 42.6, 56.2, 57.6, 65.1, 65.8, 117.3, 123.4, 126.3, 128.0, 128.6, 128.8, 130.0, 135.5, 137.1, 142.9, 147.2, 147.7, 166.3, 168.2 and 170.9.

***p*-Nitrobenzyl (6*S*,7*S*)-3-methoxy-8-oxo-7-phenylacetamido-4-oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 24**

By means of the procedure described for the preparation of compound **15**, the carbamate **23** (30 mg, 0.057 mmol) was treated with a 1 M LHMDS–THF solution (0.18 cm^3) and then with an excess of diazomethane to give *title isooxacephem* **24** as crystals (14 mg, 53%), mp 142–143 °C (from ethyl acetate–diisopropyl ether) (Found: C, 59.35; H, 4.32; N, 9.08. $C_{23}H_{21}N_3O_8$ requires C, 59.11; H, 4.53; N, 8.99%); $[\alpha]_D^{25}$ +133 (*c* 0.3, $CHCl_3$); ν_{max}(CH_2Cl_2)/cm^{-1} 1770, 1760 and 1680; δ_H(360 MHz; $CDCl_3$) 3.56 (2 H, br s, CH_2Ph), 3.86 (3 H, s, OMe), 3.89 (1 H, m, 6-H), 4.00 (1 H, dd, *J* 9.8 and 10.8, 5-H), 4.58 (1 H, dd, *J* 3.9 and 10.8, 5-H), 5.17 and 5.38 (2 H, Abq, *J* 13.7, CH_2Ar), 5.33 (1 H, dd, *J* 4.9 and 5.3, 7-H), 6.67 (1 H, d, *J* 5.3, NH), 7.22–7.35 (5 H, m, Ph), 7.57 (2 H, d, *J* 8.7, ArH) and 8.17 (2 H, d, *J* 8.7, ArH); δ_C(90 MHz; $CDCl_3$) 43.2, 47.4, 55.8, 59.0, 64.5, 69.5, 88.6, 123.6, 127.7, 128.1, 129.0, 129.2, 129.3, 133.9, 143.8, 147.6, 160.2, 161.4, 165.8 and 171.9; λ_{max}($CHCl_3$)/nm 271 (ε 32 600).

(3*S*,4*S*)-3-Azido-1-[2′,2′-diethoxy-1′-(*p*-nitrobenzylcarbamoyl)-ethyl]-4-(hydroxymethyl)azetidin-2-one 26

A solution of amino acid **4** (0.67 g, 4.2 mmol), CNPNB (0.7 g, 4.3 mmol) and diethoxyacetaldehyde (0.66 g, 5 mmol) in methanol (15 cm^3) was stirred at room temperature overnight and was then evaporated. Column chromatography of the residue (benzene–ethyl acetate, 5:1, v/v) gave *title azetidinone* **26** (1.7 g, 93%) as a 1:1 diastereomeric mixture, which could be separated by repeated flash chromatography. One isomer: ν_{max}(CH_2Cl_2)/cm^{-1} 2100, 1760 and 1670; δ_H(270 MHz; $CDCl_3$) 1.13 (3 H, t, *J* 7,6, CH_2CH_3), 1.19 (3 H, t, *J* 7.6, CH_2CH_3), 3.43 (2 H, m, 4-CH_2O), 3.75–4.03 (5 H, m, OCH_2CH_3 and OH),

4.32 (1 H, m, 4-H), 4.43 (1 H, dd, *J* 6.0 and 16.0, NHC*H*HAr), 4.60 (1 H, dd, *J* 6.0 and 16.0, NHCH*H*Ar), 4.62 (1 H, d, *J* 4.0, 1′-H), 4.86 (1 H, d, *J* 5.3, 3-H), 5.02 (1 H, d, *J* 4.0, OCHO), 7.45 (2 H, d, *J* 8.9, ArH), 8.17 (2 H, d, *J* 8.9, ArH) and 8.60 (1 H, t, *J* 6.0, NH); δ_C(67.8 MHz; $CDCl_3$) 15.1, 15.2, 42.5, 57.8, 58.8, 59.9, 64.4, 64.6, 65.2, 101.2, 123.6, 128.0, 145.6, 147.0, 166.1 and 168.1; *m*/*z*(FAB) 437 ($M^+ + 1$).

Another isomer: $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2100, 1760 and 1670; δ_H(270 MHz; $CDCl_3$) 1.20 (3 H, t, *J* 7.6, CH_2CH_3), 1.23 (3 H, t, *J* 7.6, CH_2CH_3), 3.52 (2 H, m, 4-CH_2O), 3.75–4.03 (5 H, m, OCH_2CH_3 and OH), 4.27 (1 H, m, 4-H), 4.43 (1 H, dd, *J* 5.6 and 16.0, NHC*H*HAr), 4.56 (1 H, d, *J* 5.6, 1′-H), 4.68 (1 H, dd, *J* 6.6 and 16.0, NHCH*H*Ar), 4.75 (1 H, d, *J* 5.3, 3-H), 4.94 (1 H, d, *J* 5.6, OCHO), 7.45 (2 H, d, *J* 8.9, ArH), 7.52 (1 H, br s, NH) and 8.17 (2 H, d, *J* 8.9, ArH); δ_C(67.8 MHz; $CDCl_3$) 14.9, 15.1, 42.7, 57.2, 59.6, 60.0, 62.8, 64.5, 65.0, 100.4, 123.7, 127.9, 145.3, 147.2 and 166.7; *m*/*z* (FAB) 437 ($M^+ + 1$).

p-Nitrobenzyl 2′-[(2*S*,3*S*)-3-azido-2-methylsulfonyloxymethyl-4-oxoazetidin-1-yl]-2′-2′-diethoxypropionate 27

A solution of methanesulfonyl chloride (0.5 g, 4.3 mmol) in THF (5 cm^3) was added dropwise to a solution of alcohol **26** (1.7 g, 3.9 mmol), in the form of the 1:1 isomeric mixture, and triethylamine (0.7 cm^3, 5 mmol) in THF (20 cm^3) at 0 °C. After being stirred for 1 h at room temperature, the solution was poured into ice–water (20 cm^3) and extracted with ethyl acetate. The extract was washed with brine, dried and evaporated to give the crude mesyl ester as an oil. The oil was dissolved and dry $CHCl_3$ (10 cm^3) and the solution was added to a 0.7 M N_2O_4–$CHCl_3$ solution (15 cm^3) containing sodium acetate (1.15 g, 14 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C, washed successively with aq. $NaHCO_3$ and brine, dried and evaporated. The residue was then heated in refluxing CCl_4 for 3 h. After cooling and evaporation of the solvents column chromatography of the residue (benzene–ethyl acetate, 2:1, v/v) gave *title mesyl ester* **27** as an oil (1.02 g, 57%), $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2120, 1775 and 1755; *m*/*z* (FAB) 516 ($M^+ + 1$).

p-Nitrobenzyl 2′-[(2*S*,3*S*)-3-azido-2-methylsulfonyloxymethyl-4-oxoazetidin-1-yl]-3′-hydroxypropenoate 28

Compound **27** (1.0 g, 1.9 mmol) was treated with 95% aq. TFA (5 ml) at 50 °C for 1 h. The mixture was evaporated and the residue was dissolved in ethyl acetate. The solution was washed successively with aq. $NaHCO_3$ and brine, dried and evaporated to give title compound **28** as an oil (0.68 g, 81%), which was used in the next step without further purification, ν_{max}(neat)/cm^{-1} 2120, 1760 and 1710; δ_H[360 MHz; $(CD_3)_2SO$] 3.01 (3 H, s, OMe), 4.2–4.5 (2 H, m, 2-H and 2-C*H*HOH), 4.48 (1 H, m, 2-CH*H*OH), 5.10 (1 H, d, *J* 5.1, 3-H), 5.35 (2 H, s, CH_2Ar), 7.62 (2 H, d, *J* 8.8, ArH), 7.75 ($\frac{1}{2}$H, s, vinyl H), 7.90 ($\frac{1}{2}$H, s, vinyl H) and 8.28 (2 H, d, *J* 8.8, ArH); *m*/*z* (FAB) 413 ($M^+ + 1 - CHO$).

p-Nitrobenzyl (6*S*,7*S*)-7-azido-8-oxo-4-oxa-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylate 29

Triethylamine (0.26 ml, 0.9 mmol) was added to a solution of mesyl ester **28** (0.4 g, 0.9 mmol) in CH_2Cl_2 (10 cm^3) and the solution was heated under reflux for 3 h. The solution was washed successively with ice–water, 5% hydrochloric acid, aq. $NaHCO_3$ and brine, dried and evaporated to give the *iso-oxacephem* **29** as crystals (0.3 g, 94%), which was recrystallized from ethyl acetate–diisopropyl ether to afford a pure sample, mp 149–150 °C (Found: C, 48.72; H, 3.40; N, 20.07. $C_{14}H_{11}N_5O_6$ requires C, 48.70; H, 3.21; N, 20.28%); $[\alpha]_D^{25}$ −32.2 (*c* 1.0, EtOH); ν_{max}(KBr)/cm^{-1} 2100, 1770 and 1700; δ_H(360 MHz; $CDCl_3$) 3.79 (1 H, m, 6-H), 3.94 (1 H, dd, *J* 9.5 and 11.3, 5-H), 4.60 (1 H, dd, *J* 3.7 and 11.3, 5-H), 5.27 (1 H, d, *J* 5.2, 7-H), 5.28 and 5.43 (2 H, ABq, *J* 13.5, CH_2Ar), 7.04 (1 H, s, 3-H), 7.60 (2 H, d, *J* 8.9, ArH) and 8.23 (2 H, d, *J* 8.9, ArH); δ_C(67.8 MHz; $CDCl_3$) 46.1, 65.2, 65.9, 68.2, 123.7, 128.3, 142.7, 145.8, 147.6, 161.5 and 163.5; λ_{max}(MeOH)/nm 269 (ε 16 650).

p-Nitrobenzyl (6*S*,7*S*)-7-azido-8-oxo-4-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylate 30

Methanesulfonyl chloride (0.049 g, 0.42 mmol) was added to a solution of mesyl ester **28** (0.17 g, 0.385 mmol) and triethylamine (0.062 cm^3, 0.385 mmol) in THF (10 cm^3). The mixture was stirred for 1 h at room temperature, poured into ice–water and extracted with ethyl acetate. The organic layer was washed in turn with 5% hydrochloric acid, aq. $NaHCO_3$ and brine, dried and evaporated. The remaining oil was dissolved in CH_2Cl_2 (5 cm^3) and H_2S gas was bubbled in for 3 min at 0 °C. Triethylamine (0.11 cm^3, 0.81 mmol) was added slowly and the mixture was stirred for 1 h at 5 °C. Nitrogen gas was bubbled through to remove the H_2S and the mixture was poured into ice–water. The organic layer was washed in turn with 5% hydrochloric acid, aq. $NaHCO_3$ and brine, dried and evaporated. The residue was triturated in diethyl ether to give *title isocephem* **30** as crystals (70 mg, 50%), mp 147–148 °C (from ethyl acetate–diisopropyl ether) (Found: C, 46.46; H, 3.19; N, 19.33; S, 8.86. $C_{14}H_{11}N_5O_5S$ requires C, 46.54; H, 3.07; N, 19.38; S, 8.87%); $[\alpha]_D^{25}$ −46.6 (*c* 0.5, 1,4 dioxane); ν_{max}(KBr)/cm^{-1} 2100, 1760 and 1700; δ_H(360 MHz; $CDCl_3$) 3.06 (1 H, dd, *J* 3.8 and 13, 5-H), 3.13 (1 H, dd, *J* 9.4 and 13, 5-H), 3.94 (1 H, m, 6-H), 5.22 (1 H, d, *J* 5.1, 7-H), 5.29 and 5.41 (2 H, ABq, *J* 13.0, CH_2Ar), 7.13 (1 H, s, 3-H), 7.60 (2 H, d, *J* 8.8, ArH) and 8.24 (2 H, d, *J* 8.8, ArH); δ_C(90 MHz; $CDCl_3$) 25.5, 49.2, 65.9, 68.6, 120.8, 123.3, 123.8, 142.5, 148.0, 159.6 and 161.2; λ_{max}(EtOH)/nm 302 (ε 13 200).

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