Stereocontrolled Synthesis of Piperidine-Condensed Tricyclic Carbapenems (5-Azatrinems) and Their Antibacterial Activities

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Stereocontrolled synthesis of tricyclic carbapenem (5-azatrinem) derivatives 4, in which a piperidine ring is condensed to the carbapenem skeleton, was achieved. The pivotal tricyclic intermediate 2, allyl (8*S*,9*R*,10*S*)-5-(*tert*-butoxycarbonyl)-10-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate, was synthesized starting from an acetoxyazetidinone chiron 6 in a practical manner based on a C–C bond formation reaction between 6 and piperidinone-ester 5, palladium-catalyzed de(allyloxy)carbonylation of 7b and Wittig-type cyclization *via* an oxalimide 9. Selective deprotection of the *N*-Boc group of 2 was found to proceed smoothly by treatment with trimethylsilyl trifluoromethanesulfonate and 2,6-lutidine to give the amino compound 3, whose functionalization on the nitrogen atom to derivatives 10 followed by deprotection led to various 5-azatrinem acids 4. These compounds showed potent *in vitro* activities against gram-positive and gram-negative bacteria.

Key words carbapenem; trinem; antibacterial activity; synthesis; azatrinem; intramolecular Wittig-type reaction

Since the discovery of thienamycin in 1976 by the Merck research group,[1] a huge number of carbapenem derivatives have been synthesized with the development of new synthetic methodologies for seeking potent antibacterial agents.[2] With the growing concern over the emergence of antibiotic-resistant bacteria, some structurally unique carbapenem analogs have been explored to overcome this serious problem. For this goal, tricyclic carbapenems (referred to as trinems), such as Sanfetrinem, which has a fused cyclohexane ring possessing a 4α-methoxy substituent (Fig. 1, X=OCH_3), were reported by the Glaxo Wellcome research group.[3] In a further study of the trinem series,[4] some thia- or oxa-analogs containing a sulfur or an oxygen atom in the cyclohexane ring, that is 4-, 6- and 7-thia-trinem, or 5- and 7-oxo-analogs have also been synthesized and their antibacterial activities have been reported.[5] However, there have been no reports on the corresponding aza-analog.[6] We were particularly interested in 5-azatrinems, because there were only a few reports on 5-substituted trinem derivatives[7] and introduction of a nitrogen atom at the 5-position is convenient for modifying the molecule at this position. Therefore our principal aim in this project was to develop an efficient synthetic route to 5-azatrinems and to evaluate these compounds as possible antibacterial agents.

Here we report a stereocontrolled synthesis of a piperidine-condensed tricyclic key intermediate **2** which is suitable *via* **3** for modification on the nitrogen atom, its subsequent derivatization to a variety of 5-azatrinems **4** and their *in vitro* antibacterial activities.

Synthesis Analysis of our target structure led us to prepare a 3-azacyclohexanone derivative **1**, which has the same configuration at the C-8 position as trinem, utilizing a stereocontrolled decarboxylation reaction of a β-ketoester **7b** according to a literature procedure.[8] A coupling reaction of the commercially available acetoxyazetidinone **6** with the sodium salt of allyl β-ketoester **5**, which was provided by the transesterification reaction of the corresponding ethyl ester with sodium allyloxide in allyl alcohol, in tetrahydrofuran (THF) gave a 3 : 2 mixture of two diastereoisomers **7a** in quantitative yield. After protecting the NH group of **7a** by treatment with *tert*-butyldimethylsilyl triflate (TBSOTf) and 2,6-lutidine in dichloromethane (CH_2Cl_2), the product **7b** was subjected to the stereocontrolled decarboxylation reaction in the presence of triethylamine (Et_3N), formic acid and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in ethyl acetate (EtOAc).[9] The reaction occurred readily at 0 °C to afford the ketone **8a** with desired stereochemistry[10] in 77% yield from **7a**. The ketone **8a** was not stable enough, probably due to its basicity, to store for weeks in a refrigerator even in a crystalline form. Therefore, the *N*-benzyl group was exchanged to the *N*-*tert*-butoxycarbonyl (*N*-Boc) group as follows. Hydrogenolysis of **8a** using 10% Pd–charcoal under a hydrogen atmosphere in EtOAc in the presence of di-*tert*-butyl dicarbonate (Boc_2O) gave a quantitative yield of **8b**. The ketone **8b** was stable in cold storage, but it was found to be sensitive to silica gel, on which chromatography brought about partial epimerization at the α-position of the ketone group. This epimerization was also observed in the next reaction to deprotect the *N*-TBS group of **8b**. The results of *N*-desilylation of **8b** with tetrabutylammo-

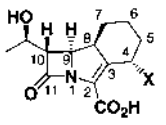

Fig. 1. General Structure of Trinem Template

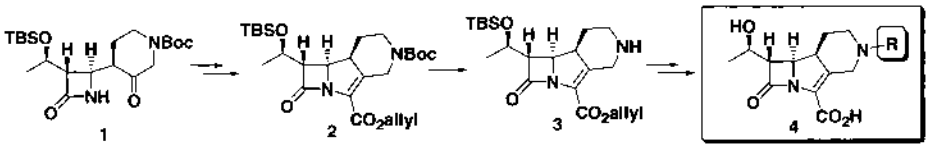

Chart 1

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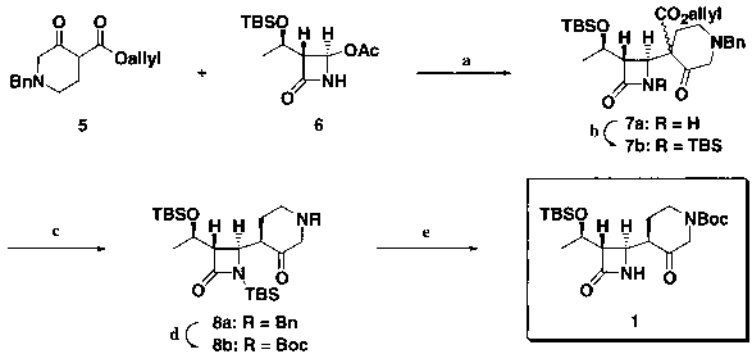
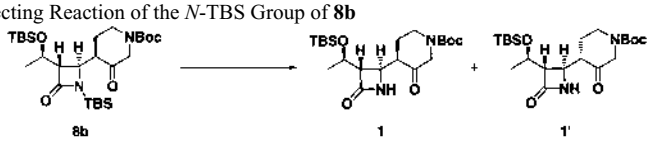


(a) NaH, THF, 0 °C; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2; (c) HCO_2H, Et_3N, $Pd(PPh_3)_4$, PPh_3, EtOAc, 0°C; (d) Boc_2O, H_2, Pd(C), EtOAc; (e) TBAF, 1 N HCl, THF–H_2O, 0 °C.

Chart 2

Table 1. The Product Ratio in Deprotecting Reaction of the *N*-TBS Group of **8b**



Run	Reagents (eq)	Solvent	Temp./°C	Time/h	Ratio (**1** : **1′**)[a]
1	TBAF(1.0)	THF	0	0.1	Decomposition
2	TBAF(1.0)–AcOH(1.0)	THF	0	1	1 : 1
3	TBAF(1.0)–AcOH(2.0)	THF	0	1	2.2 : 1
4	TBAF(1.0)–HCO_2H(2.0)	THF	r.t.	1	3.2 : 1
5	TBAF(1.0)–HCO_2H(5.0)	THF	r.t.	1	3.7 : 1
6	TBAF(1.0)–HF(2.0)	THF–H_2O (10 : 1)	0	1	4.3 : 1
7	TBAF(1.0)–HCl(1.0)	THF–H_2O (10 : 1)	0	2.5	10 : 1

a) The ratio was determined by ^{1}H-NMR spectrum of the crude product.

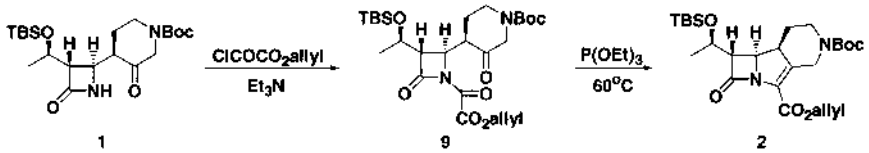


Chart 3

nium fluoride (TBAF) in the presence of various acids are summarized in Table 1. Treatment of **8b** with TBAF (1 eq) in the presence of AcOH (1 eq) in THF (run 2) gave a 1 : 1 mixture of **1** and its epimer **1′**. Use of excess acid retarded the epimerization. Hydrogen fluoride gave better results than organic acids. The best result was obtained by using a combination of TBAF (1 eq) and HCl (1 eq) to give a 10 : 1 ratio of **1** : **1′** (run 7).

The ketone **1** also isomerized during silica gel chromatography. Fortunately, the crude product crystallized without chromatography and it could be purified by recrystallization from hexane to afford the pure ketone **1** in 66% yield in two steps from **8a**, which was found to be stable during storage at room temperature. The ketone **1** could be transformed to the piperidine-condensed tricyclic compound **2** in a conventional manner *via* an intramolecular Wittig-type reaction[11] as follows. Treatment of **1** with allyloxyoxalyl chloride in the presence of Et_3N in CH_2Cl_2 afforded the oxalimide **9**, which was then heated with excess triethyl phosphite in toluene at 60 °C for 3 h. The ylide formation and subsequent cyclization occurred simultaneously at this temperature and the pure crystals of **2** were obtained in 67% yield by recystallization of the crude product. The stereochemistry at the C8 position of **2** was confirmed by nuclear Overhauser effect (NOE) experiment. The NOEs were observed between 8-H and 9-H, and 7-H and 10-H, respectively.

With the precursor **2** of 5-azatrinem derivatives in hand, we investigated the selective deprotection of its *N*-Boc group to provide the NH compound **3**. The 5-azatrinem skeleton could not survive under the usual acidic conditions to deprotect the *N*-Boc group. Recently, TBSOTf/2,6-lutidine or trimethylsilyl triflate (TMSOTf)/2,6-lutidine has been reported as an efficient reagent for chemoselective removal of the *N*-Boc group.[12] We applied this procedure to our sensitive compound. Treatment of **2** with 1.2 eq of TMSOTf in the presence of 2,6-lutidine (1.2—1.5 eq) in CH_2Cl_2 at 0 °C to room temperature for 10—15 min and subsequent aqueous workup afforded a free piperidine derivative **3** in quantitative yield. This amine was not stable. So, it was immediately transformed to a variety of *N*-modified precursors **10** for azatrinems such as amides, amines, ureas, thiourea, and amidines by reaction with various electrophiles as shown in

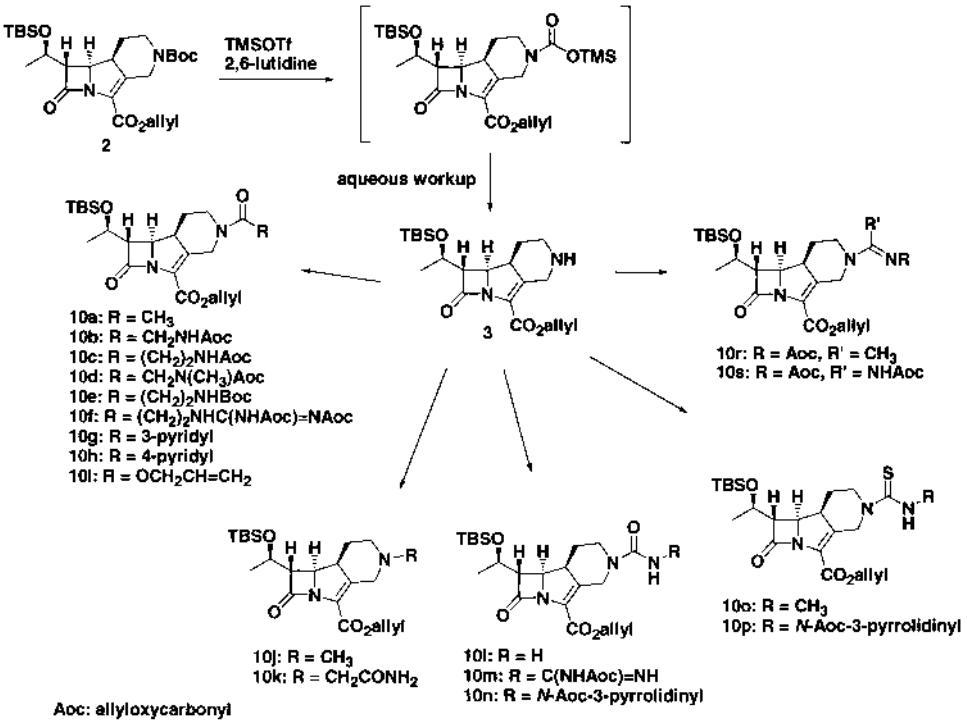
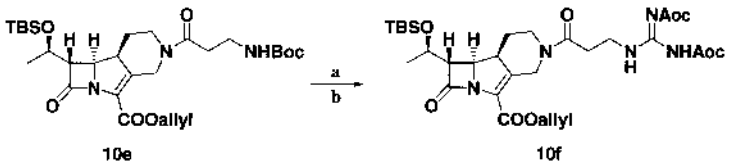
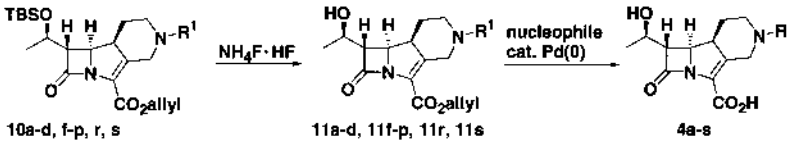


Chart 4



(a) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C-rt; (b) *N,N'*-bis(Aoc)amidinopyrazole, THF, r.t.

Chart 5



	R^1 (for 10 and 11)
a	$COCH_3$
b	$COCH_2NHAoc$
c	$CO(CH_2)_2NHAoc$
d	$COCH_2N(CH_3)Aoc$
e	$CO(CH_2)_2NHBoc$
f	$CO(CH_2)_2NHC(NHAoc)=NAoc$
g	CO-4-pyridyl
h	CO-3-pyridyl
i	Aoc
j	CH_3
k	CH_2CONH_2
l	$CONH_2$
m	$CONHC(NHAoc)=NH$
n	CO-N-Aoc-3-pyrrolidinyl
o	$CSNHCH_3$
p	CS-N-Aoc-3-pyrrolidinyl
r	$C(CH_3)=NAoc$
s	C(NAoc)=NAoc

	R (for 4)
a	$COCH_3$
b	$COCH_2NH_2$
c	$CO(CH_2)_2NH_2$
d	$COCH_2NH(CH_3)$
e	$COCH_2N(CH_3)CH=NH$
f	$CO(CH_2)_2NHC(NH_2)=NH$
g	CO-4-pyridyl
h	CO-3-pyridyl
i	H
j	CH_3
k	CH_2CONH_2
l	$CONH_2$
m	$CONHC(NH_2)=NH$
n	CO-NH-3-pyrrolidinyl
o	$CSNHCH_3$
p	CS-NH-3-pyrrolidinyl
q	CH=NH
r	$C(CH_3)=NH$
s	C(NH)=NH

Chart 6

Chart 4.

The amide-type precursors **10a**—**e**, **g**, **h** were synthesized by treatment of **3** with the corresponding acid chloride or acylimidazolide. A precursor **10i** for unsubstituted 5-azatrinem **4i** (R=H) was obtained by reaction of **3** with allyl chloroformate. 3-Guanidinopropionyl derivative **10f** was prepared from **10e** as follows (Chart 5). The *N*-Boc group of **10e** was removed by use of the above mentioned TMSOTf/2,6-lutidine combination and subsequent treatment with *N*,*N*′-bis(allyloxycarbonyl)amidinopyrazole[13] afforded **10f**. *N*-Alkylation of **3** with alkyl iodide in the presence of triethylamine or potassium carbonate afforded the tertiary amines **10j**, **k**. The ureas **10l**, **n** were synthesized by treatment of **3** with trimethlysilyl isocyanate and 3-isocyanato-*N*-Aoc-pyrrolidine, respectively. On the other hand, **10m** was prepared by reaction of the piperidine **3** with triphosgene, followed by treatment with *N*-Aoc-guanidine, in the presence of 4-dimethylaminopyridine (DMAP). The thioureas **10o**, **p** were synthesized by treatment of **3** with isothiocyanates, which were prepared by reaction of 1,1′-thiocarbonyldiimidazole and primary amines. The amidine precursor **10r** and guanidine precursor **10s** were synthesized by treatment of **3** with *N*-(allyloxycarbonyl)acetamidine hydrochloride and *N*,*N*′-bis(allyloxycarbonyl)amidinopyrazole, respectively.

The 5-azatrinem precursors **10** thus obtained could be transformed to the fully deprotected acids **4** in 2 steps. Firstly, the TBS protecting group of **10** was removed by treatment with NH_4F HF in a 1 : 1 mixture of *N*,*N*′-dimethylformamide (DMF) and *N*-methylpyrrolidinone[14] to give the alcohols **11** in moderate yields. Then, the allyl ester group and/or *N*-allyloxycarbonyl group(s) in the side chain of **11** were deprotected by Pd(0) catalyzed deallylation reaction[15] in the presence of a suitable allyl scavenger such as dimedone, potassium 2-ethylhexanoate or *n*-butyltin hydride to give the piperidine-condensed tricyclic carbapenems **4** (Chart 6). Amidines **4e** and **4q** were prepared by formimidoylation of the amines **4d** and **4i**, respectively, with excess benzyl formimidate hydrochloride in a buffered aqueous acetonitrile in the presence of *N*,*N*′-diisopropylethylamine.

Biological Properties The *in vitro* antibacterial activities (minimal inhibitory concentrations (MICs)) of these 5-azatrinems (**4a**—**s**) are shown in Table 2. Among amide-type derivatives **4a**—**h**, 5-acetyl derivative **4a** has reasonable antibacterial potency, although its activity was generally weaker than Sanfetrinem. The pyridylcarbonyl compounds **4g**, **h** showed decreased activity. Introduction of the amino, amidino or guanidino function on the acyl side chain as shown such as glycine and *β*-alanine analogs **4b**—**f** improved potency against both gram-positive and -negative bacteria. But they have weak activity against *Proteus vulgaris*, *Morganella morganii* and methicillin-resistant-*staphylococcus aureus* (MRSA). The simple amines **4i** and **4j**, whose nitrogen atom in the piperidine ring is basic, showed less antibacterial activity than glycine and *β*-alanine analogs **4b**—**f**. The *tert*-amine derivative **4k** with the methyl group modified by the carbamoyl group recovered some antibacterial activities in contrast to **4j**, probably due to the hydrophilic property of the carbamoyl group and increased stability of the compound coming from the decreased basicity by attaching the electron-withdrawing group. In a series of urea and thiourea compounds **4l**—**p**, the simple urea **4l** and the guani-

Table 2. Antibacterial Activity (MIC, *μ*g/ml)[a] of Azatrinems **4a**—**s** and Sanfetrinem (GV104326)

	Sanfetrinem	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**	**4j**	**4k**	**4l**	**4m**	**4n**	**4o**	**4p**	**4q**	**4r**	**4s**
Staphylococcus aureus 209P	0.02	0.1	0.05	0.1	0.05	0.1	0.02	0.4	1.5	0.05	0.1	0.02	0.1	0.02	0.2	0.2	0.1	<0.01	<0.01	<0.01
S. aureus 56R	0.05	0.2	0.1	0.2	0.2	0.4	0.1	0.8	1.5	0.2	0.4	0.1	0.2	0.02	0.8	0.4	0.4	0.02	0.05	0.02
S. aureus 535 (MRSA)	12.5	25	100	100	>100	>100	25	25	100	50	50	100	25	12.5	>100	50	100	12.5	12.5	6.2
Enterococcus faecalis 681	0.8	3.1	1.5	1.5	1.5	3.1	1.5	6.2	25	25	50	6.2	1.5	1.5	6.2	6.2	6.2	0.8	1.5	0.4
Escherichia coli NIHJ	0.2	0.1	0.1	0.2	0.2	0.8	0.2	0.8	3.1	3.1	3.1	0.4	0.05	0.1	0.8	0.4	3.1	0.1	0.2	0.1
E. coli 609	1.5	0.8	12.5	1.5	12.5	3.1	0.8	6.2	25	25	25	6.2	1.5	0.8	12.5	3.1	50	0.8	0.8	3.1
Salmonella enteritidis	0.2	0.2	0.2	0.4	0.8	1.5	0.2	1.5	6.2	6.2	12.5	0.8	0.4	0.4	1.5	0.4	6.2	0.4	0.4	0.2
Klebsiella pneumoniae 806	0.4	0.2	0.2	0.4	0.2	0.8	0.2	0.8	3.1	3.1	6.2	0.8	0.1	0.2	1.5	0.4	6.2	0.2	0.4	0.2
K. pneumoniae 846	1.5	0.2	0.1	0.2	0.2	0.4	0.2	6.2	25	3.1	6.2	0.8	0.2	0.4	0.8	12.5	100	0.1	0.2	0.1
Enterobacter cloacae 903	6.2	3.1	25	12.5	25	12.5	3.1	25	100	50	50	6.2	3.1	1.5	12.5	12.5	50	3.1	6.2	3.1
Serratia marcescens 1184	0.8	0.2	0.2	0.4	0.4	0.8	0.4	1.5	6.2	6.2	12.5	1.5	0.1	0.2	1.5	0.8	25	0.4	0.4	0.2
Proteus vulgaris 1420	0.4	12.5	>100	100	>100	>100	25	25	50	>100	>100	100	25	12.5	100	12.5	>100	50	100	50
Morganella morganii 1510	0.8	12.5	>100	100	>100	>100	25	50	100	>100	>100	50	12.5	12.5	100	12.5	>100	50	50	50
Pseudomonas aeruginosa 1001	100	>100	6.2	12.5	6.2	25	12.5	>100	>100	25	100	>100	>100	50	>100	>100	>100	3.1	6.2	3.1

a) MIC was determined by the agar dilution method with an inoculum of 10^7 cfu/ml.

dinocarbonyl derivative **4m** exhibited potent and broad-spectrum activity comparable to Sanfetrinem. None of these azatrinems showed any interesting antibacterial activity against *Pseudomonas aeruginosa*. The amidine and guanidine derivatives **4q**—**s** showed a good potency against gram-positive and -negative bacteria. In particular, the formamidine **4p** and guanidine **4s** expressed high activity with a well-balanced spectrum including activity against *P. aeruginosa*. This antipseudomonal activity supports the hypothesis that a positively charged functional group facilitates the penetration of β-lactams into *Pseudomonas* spp.[4] In order to estimate the biological stability of the 5-azatrinem, urinary recovery of the formimidoyl compound **4q** was determined by subcutaneous administration to mice. Forty-seven percent of the 5-formimidoyl-5-azatrinem **4q** was recovered in urine.

Conclusion

The convenient 5-azatrinem precursor **2** was synthesized starting from an acetoxyazetidinone **6** in a practical manner based on stereocontrolled palladium-catalyzed de(allyloxy)-carbonylation and Wittig-type cyclization *via* an oxalimide **9**. Selective deprotection of the *N*-Boc group of **2** by treatment with TMSOTf and 2,6-lutidine to give the amino compound **3**, whose functionalization on the nitrogen atom to derivatives **10** followed by deprotection led to various 5-azatrinem analogs **4**. In the course of our study for seeking 5-azatrinem derivatives that show potent antibacterial activities, we found 5-amidino-type compounds that possessed potent *in vitro* activities against gram-positive and -negative bacteria.

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL JNM-EX-270 (270 MHz) or a JEOL JNM-GX-270 (270 MHz) spectrometer and ^{13}C-NMR spectra were recorded on a JEOL JNM-GSX-400 (100 MHz) spectrometer. Chemical shifts are shown in ppm downfield from internal tetramethylsilane in $CDCl_3$ or sodium 2,2-dimethyl-2-silapentane-5-sulfonate in D_2O. The abbreviations used in the ^{1}H-NMR data are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dq, doublet of quartets; br, broad; m, multiplet. Infrared (IR) spectra were recorded on a JASCO A-102, FT/IR-8300 or FT/IR-8900 spectrometer. Optical rotations were measured on a Perkin-Elmer 141 spectrometer at 25 °C. Mass spectra (MS) were obtained on a JEOL JMS-D300 or JMS-AX505H spectrometer. Chromatography columns were prepared with Silica gel 60 (230—400 mesh, E. Merck) or Cosmosil 75C_{18}-PREP (Nacalai Tesque). High pressure liquid chromatography (HPLC) was performed on an LC-908 (Japan Analytical Industry Co., Ltd.) with joined two GPC columns in succession (a JAIGEL-1H (20 mm i.d.×600 mm) and a JAIGEL-2H (20 mm i.d.×600 mm)).

***N*-(Allyloxycarbonyl)amino Acids** *N*-(allyloxycarbonyl)amino acids were prepared from the corresponding amino acids following the literature procedure.[15d] The preparation of 3-(allyloxycarbonylamino)propionic acid is described below as a typical example. To a solution of 3-aminopropionic acid (5.0 g, 5.6×10^{-2} mol) in a mixture of H_2O–THF (2 : 1, 90 ml) were added a solution of allyl chloroformate (5.9 ml, 5.6×10^{-2} mol) in THF (30 ml) and 2 N NaOH (56 ml) at room temperature. After being stirred for 1 h, the mixture was concentrated under reduced pressure to *ca.* 30 ml and then acidified to *ca.* pH 2 by addition of 2 N HCl. The product was extracted with EtOAc. The extract was dried and concentrated under reduced pressure to give 3-(allyloxycarbonylamino)propionic acid (9.68 g) as a colorless oil in quantitative yield. ^{1}H-NMR ($CDCl_3$) δ: 2.61 (2H, br t, J=6 Hz), 3.47 (2H, br q, J=6 Hz), 4.56 (2H, d, J=5 Hz), 5.22 (1H, d, J=10 Hz), 5.31 (1H, d, J=17 Hz), 5.35 and 6.39 (1H, br s×2), 5.91 (1H, ddt, J=17, 19, 5 Hz), 10.81 (1H, m).

N-Allyloxycarbonylsarcosine was prepared in a similar manner in 93% yield as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.01 (3H, s), 4.00—4.15 (2H, m), 4.55—4.65 (2H, m), 5.15—5.40 (2H, m), 5.80—6.05 (1H, m), 8.40 (1H, br s). These products were used for the next reaction without further purification.

Allyl 1-Benzyl-3-oxo-4-piperidinecarboxylate (5) A solution of ethyl 1-benzyl-3-oxo-4-piperidinecarboxylate (22.0 g, 8.42×10^{-2} mol) in allyl alcohol (50 ml) was added to a solution of sodium allyloxide, prepared by dissolving sodium stick (2.1 g, 9.1×10^{-2} mol) in allyl alcohol (200 ml), with stirring at 0 °C, and the mixture was heated under reflux for 10 h. After being cooled, the reaction mixture was slowly poured into ice-cold 1 N HCl (200 ml), and then neutralized by addition of a saturated aqueous solution of $NaHCO_3$. The product was extracted with EtOAc, and the extract was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (400 g) using a mixture of hexane and EtOAc (5 : 1) as eluent to give **5** (14.2 g, 62%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (2H, t, J=5.8 Hz), 2.59 (2H, t, J=5.8 Hz), 3.11 (2H, s), 3.61 (2H, s), 4.67 (2H, br t, J=5.4 Hz), 5.24 (1H, dd, J=10.5, 1.2 Hz), 5.33 (1H, dd, J=17.2, 1.6 Hz), 5.93 (1H, ddt, J=17.2, 10.5, 5.4 Hz), 7.32 (1H, s). IR (neat): 1736, 1665, 1626 cm^{-1}.

(3*S*,4*R*)-4-[4-(Allyloxycarbonyl)-1-benzyl-3-oxopiperidin-4-yl]-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (7a) To a suspension of sodium hydride (55% mineral oil dispersion, 3.60 g, 82.5 mmol, washed with hexane) in THF (75 ml) was added a solution of **5** (20.5 g, 75.0 mmol) in THF (75 ml) at 0 °C and the mixture was stirred at room temperature for 30 min. After the mixture was cooled at 0 °C, a solution of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*tert*-butyldimethylsilyl)ethyl]-2-azetidinone (**6**, 21.55 g, 74.98 mmol) in THF (150 ml) was added. After being stirred at 0 °C for 30 min, the mixture was partitioned between a diluted aqueous solution of ammonium chloride (100 ml) and EtOAc (50 ml). The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (400 g) using a mixture of hexane and EtOAc (3 : 1) as eluent, to give **7a** (37.0 g, 99%) as a colorless oil which was shown by ^{1}H-NMR spectrum to be a 3 : 2 mixture of two diastereoisomers.

Major Isomer: *Rf* 0.36 (hexane : EtOAc=2 : 1). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.19 (3H, d, J=6.2 Hz), 1.6—1.8 (1H, m), 2.5—2.8 (3H, m), 3.02 (1H, d, J=16.3 Hz), 3.20 (1H, m), 3.23 (1H, d, J=16.3 Hz), 3.51 (1H, d, J=13.1 Hz), 3.59 (1H, d, J=13.1 Hz), 3.87 (1H, d, J=2.2 Hz), 4.1—4.2(1H, m), 4.59 (1H, dd, J=13.0, 6.0 Hz), 4.69 (1H, dd, J=13.0, 6.0 Hz), 5.23 (1H, d, J=10.5 Hz), 5.25 (1H, dd, J=17.0 Hz), 5.81 (1H, ddt, J=17.0, 10.5, 6.0 Hz), 5.95 (1H, br s), 7.2—7.4 (5H, m). IR ($CHCl_3$): 3421, 1764, 1719 cm^{-1}. MS (FAB) *m/z*: 501 $(M+H)^+$.

Minor Isomer: *Rf* 0.25 (hexane : EtOAc=2 : 1). ^{1}H-NMR ($CDCl_3$) δ: 0.06 (6H, s), 0.87 (9H, s), 1.00 (3H, d, J=6.5 Hz), 1.9—2.1 (1H, m), 2.5—2.7 (2H, m), 2.8—2.9 (1H, m), 2.94 (1H, d, J=16.8 Hz), 3.03 (1H, br t, J=2.4 Hz), 3.27 (1H, br d, J=16.8 Hz), 3.51 (1H, d, J=13.2 Hz), 4.23 (1H, dq, J=6.5, 2.6 Hz), 4.36 (1H, d, J=2.2 Hz), 4.5—4.8 (2H, m), 5.26 (1H, dd, J=10.5, 1.2 Hz), 5.30 (1H, dd, J=17.2, 1.2 Hz), 5.67 (1H, br s), 5.84 (1H, ddt, J=17.2, 10.5, 5.9 Hz), 7.2—7.4 (5H, m). IR ($CHCl_3$): 3166, 3098, 1765, 1726 cm^{-1}. MS (FAB) *m/z*: 501 $(M+H)^+$.

(3*R*,4*S*)-4-[(*R*)-1-Benzyl-3-oxopiperidin-4-yl]-1-(*tert*-butyldimethylsilyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (8a) To a solution of **7a** (37.0 g, 7.39×10^{-2} mol) and 2,6-lutidine (18.9 ml, 8.25×10^{-2} mol) in CH_2Cl_2 (250 ml) was added TBSOTf (9.7 ml, 8.3×10^{-2} mol) at 0 °C. After being stirred for 10 min, water and a mixture of EtOAc and hexane (4 : 1, 750 ml) were added to the reaction mixture. The organic layer was separated, washed with a saturated aqueous solution of $NaHCO_3$, a saturated aqueous solution of NH_4Cl and brine, successively, and dried. After evaporation of the solvent, the crude product was subjected to chromatography on silica gel (400 g) using a mixture of hexane and EtOAc (4 : 1) as eluent, to give the *N*-TBS-protected product **7b** as a colorless oil (47 g). A solution of **7b** in EtOAc (250 ml) was added to a mixture of tetrakis(triphenylphosphine)palladium (867 mg, 7.50×10^{-4} mol), triphenylphosphine (984 mg, 3.75×10^{-3} mol), Et_3N (36.7 ml, 2.63×10^{-1} mol) and formic acid (8.49 ml, 2.25×10^{-1} mol) in EtOAc (300 ml) at 0 °C. The mixture was stirred at the same temperature for 2.5 h, diluted with hexane (200 ml), and washed with a saturated aqueous solution of NH_4Cl (200 ml×3), water (200 ml), and brine (200 ml×2), dried, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (1.2 kg) using a mixture of ethyl acetate and hexane (1 : 5 to 1 : 1) as eluent to give the product **8a** (30.1 g, 77%) as pale yellow crystals, mp 96—99 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.07 (3H, s), 0.08 (3H, s), 0.29 (3H, s), 0.85 (9H, s), 0.95 (9H, s), 1.25 (3H, d, J=6.0 Hz), 1.8—2.1 (2H, m), 2.4—2.6 (2H, m), 2.72 (1H, d, J=14.8 Hz), 2.94 (1H, dd, J=7.9, 2.7 Hz), 3.06 (1H, br d, J=11 Hz), 3.28 (1H, dd, J=14.8, 1.5 Hz), 3.54 (1H, d, J=13.2 Hz), 3.63 (1H, d, J=13.2 Hz), 4.07 (1H, dq, J=7.9, 6.0 Hz), 4.23 (1H, m), 7.2—7.4 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: −5.1, −4.8, −4.6, −4.4, 17.9, 19.0, 22.9, 24.5, 25.8 (3C), 26.4 (3C), 49.8, 51.6, 51.9, 61.9, 62.4,

64.5, 67.8, 127.4, 128.4 (2C), 128.8 (2C), 137.2, 173.3, 205.1. IR (KBr): 2953, 2930, 2886, 2858, 1733, 1718 cm^{-1}.

(3*R*,4*S*)-4-[(*R*)-1-(*tert*-Butoxycarbonyl)-3-oxopiperidin-4-yl]-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (1) A solution of **8a** (30.0 g, 5.65×10^{-2} mol) and di-*tert*-butyldicarbonate (13.0 g, 5.96×10^{-2} mol) in EtOAc (300 ml) was stirred with 10% Pd–C (10 g) under a hydrogen atmosphere at room temperature for 4 h. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in THF (150 ml), and a mixture of 1 N HCl (55 ml) and 1 M TBAF THF solution (57 ml) was added at 0 °C. After being stirred at 0 °C for 1.5 h, the mixture was quenched by addition of phosphate buffer (200 ml) and extracted with EtOAc (400 ml). The extract was washed with a saturated aqueous solution of $NaHCO_3$, a saturated aqueous solution of NH_4Cl, and then brine. The organic layer was dried and concentrated under reduced pressure to give a pale yellow oil, which was purified by recrystallization from hexane to give **1** (15.8 g, 66%) as colorless crystals, mp 139—142 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (3H, s), 0.08 (3H, s), 0.87 (9H, s), 1.24 (3H, d, J=6.2 Hz), 1.47 (9H, s), 1.75—1.95 (1H, m), 2.10—2.25 (1H, m), 2.60—2.70 (1H, m), 2.93 (1H, dd, J=4.9, 2.5 Hz), 3.50—3.70 (1H, m), 3.80—3.95 (1H, m), 3.97 (1H, d, J=17.8 Hz), 4.09 (1H, d, J=17.8 Hz), 4.15—4.30 (2H, m), 5.67 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: −5.0, −4.2, 18.0, 22.6, 23.1, 25.8 (3C), 28.3 (3C), 41.7, 48.5, 49.7, 54.3, 60.9, 65.8, 80.9, 154.4, 168.4, 206.0. IR (KBr): 3265, 2956, 2931, 2887, 2858, 1762, 1721, 1682 cm^{-1}. $[\alpha]_D^{25}$ +34° (c=0.74, $CHCl_3$). *Anal.* Calcd for $C_{21}H_{38}N_2O_5Si$: C, 59.12; H, 8.98; N, 6.57. Found: C, 58.92; H, 9.01; N, 6.53. MS (FAB) m/z: 427 $(M+H)^+$. **1′** (Epimer of **1**): ^{1}H-NMR ($CDCl_3$) δ: 0.06 (3H, s), 0.07 (3H, s), 0.88 (9H, s), 1.23 (3H, d, J=6.2 Hz), 1.47 (9H, s), 1.55—1.80 (1H, m), 2.10—2.25 (1H, m), 2.45 (1H, ddd, J=12.9, 9.6, 5.7 Hz), 2.76 (1H, m), 3.30—3.50 (1H, m), 3.62 (1H, dd, J=9.6, 2.0 Hz), 3.80—4.05 (1H, m), 3.90 (1H, br d, J=18 Hz), 4.15 (1H, d, J=17.8 Hz), 4.10—4.25 (1H, m), 6.19 (1H, br s).

Allyl (8*S*,9*R*,10*S*)-5-(*tert*-Butoxycarbonyl)-10-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (2) To a solution of **1** (3.75 g, 8.79×10^{-3} mol) in CH_2Cl_2 (37 ml) were added Et_3N (1.84 ml, 1.32×10^{-2} mol) and allyloxyoxalyl chloride (1.96 g, 1.32×10^{-2} mol), successively, at −78 °C. After being stirred at 0 °C for 10 min, the mixture was quenched with phosphate buffer and extracted with EtOAc (400 ml). The extract was washed with water, a saturated aqueous solution of $NaHCO_3$, a saturated aqueous solution of NH_4Cl and brine, successively. The organic layer was dried and concentrated under reduced pressure to give **9** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (3H, s), 0.08 (3H, s), 0.85 (9H, s), 1.23 (3H, d, J=6 Hz), 1.47 (9H, s), 1.70—1.90 (1H, m), 2.05—2.20 (1H, m), 3.10 (1H, dt, J=13, 5 Hz), 3.22 (1H, t, J=4 Hz), 3.30—3.50 (1H, m), 3.90—4.10 (1H, m), 3.92 (1H, d, J=18 Hz), 4.16 (1H, d, J=18 Hz), 4.31 (1H, qd, J=6, 4 Hz), 4.51 (1H, t, J=4 Hz), 4.80 (2H, d, J=6 Hz), 5.32 (1H, d, J=11 Hz), 5.41 (1H, dd, J=17, 1 Hz), 5.97 (1H, ddt, J=17, 10, 6 Hz). IR ($CHCl_3$): 1810, 1754, 1727, 1695 cm^{-1}. This crude oil was dissolved in toluene (4 ml) and triethyl phosphite (12 ml) was added, and the whole was heated at 60 °C for 3 h. After removal of excess triethyl phosphite and solvent under reduced pressure, the residue was subjected to column chromatography on silica gel (100 g) using a mixture of hexane and EtOAc (4 : 1) as eluent. The eluate was concentrated under reduced pressure to give a pale yellow oil, which was crystallized from hexane to give **2** (3.03 g, 67%) as colorless crystals, mp 86—89 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.22 (3H, d, J=6.1 Hz), 1.46 (9H, s), 1.50—1.70 (1H, m), 1.75—1.90 (1H, m), 2.86 (1H, br t, J=12.0 Hz), 2.99 (1H, td, J=12.0, 5.0 Hz), 3.22 (1H, dd, J=5.2, 3.6 Hz), 3.51 (1H, br d, J=14.8 Hz), 4.15—4.20 (1H, m), 4.24 (1H, dd, J=6.5, 3.6 Hz), 4.20—4.40 (1H, m), 4.70 (1H, br dd, J=13.4, 5.4 Hz), 4.81 (1H, br dd, J=13.4, 5.4 Hz), 5.26 (1H, dd, J=10.5, 1.2 Hz), 5.43 (1H, dd, J=17.2, 1.5 Hz), 5.62 (1H, d, J=14.8 Hz), 5.97 (1H, ddt, J=17.2, 10.5, 5.4 Hz). ^{13}C-NMR ($CDCl_3$) δ: −4.9, −4.2, 18.0, 22.4, 25.7 (3C), 28.4 (3C), 28.8, 42.9, 43.0, 46.0, 54.7, 61.8, 65.7, 66.1, 76.7, 80.4, 118.5, 125.8, 131.5, 140.3, 154.5, 160.6, 176.8. IR (KBr): 2977, 2951, 2930, 2858, 1777, 1715, 1699, 1649 cm^{-1}. $[\alpha]_D^{25}$ +104° (c=0.85, $CHCl_3$). *Anal.* Calcd for $C_{26}H_{42}N_2O_6Si$: C, 61.63; H, 8.36; N, 5.53. Found: C, 61.69; H, 8.56; N, 5.56. MS (FAB) m/z: 507 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-10-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (3) To a solution of **2** (600 mg, 1.18×10^{-3} mol) and 2,6-lutidine (206 μl, 1.77×10^{-3} mol) in CH_2Cl_2 (6 ml) was added TMSOTf (284 μl, 1.47×10^{-3} mol) at 0 °C. After being stirred at the same temperature for 15 min, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with EtOAc. The extract was washed with brine, dried and concentrated under reduced pressure to give **3** (440 mg, 91%) as a pale yellow oil, which was immediately used for the next reaction without further purification due to its instability. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.24 (3H, d, J=6.2 Hz), 1.57 (1H, qd, J=12, 4 Hz), 1.50—1.80 (1H, m), 1.85—1.95 (1H, m), 2.79 (1H, ddd, J=14, 12, 2 Hz), 2.97 (1H, br td, J=12, 5 Hz), 3.18 (1H, dd, J=6.4, 3.5 Hz), 3.24 (1H, br d, J=14 Hz), 3.36 (1H, d, J=14.2 Hz), 4.17 (1H, dd, J=10.4, 3.5 Hz), 4.15—4.20 (1H, m), 4.68 (1H, dd, J=13.5, 5.4 Hz), 4.78 (1H, dd, J=13.5, 5.4 Hz), 5.25 (1H, d, J=10.6 Hz), 5.42 (1H, br d, J=17.0 Hz), 5.93 (1H, ddt, J=17.0, 10.6, 5.4 Hz).

Allyl (8*S*,9*R*,10*S*)-5-Acetyl-10-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10a) To a solution of the above-mentioned crude product **3** (217 mg, 5.34×10^{-4} mol) and Et_3N (117 μl, 0.84×10^{-4} mol) in CH_2Cl_2 (2.5 ml) was added acetyl chloride (57 μl, 8.0×10^{-4} mol) at 0 °C. After being stirred for 15 min, the mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH_4Cl, a saturated aqueous solution of $NaHCO_3$, and then brine. The organic layer was dried and concentrated under reduced pressure. The residue was subjected to HPLC using $CHCl_3$ as eluent to afford **10a** (208 mg, 87%) a colorless crystals, mp 49—54 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.21 (3H, d, J=6.2 Hz), 1.45—1.70 (1H, m), 1.80—2.00 (1H, m), 2.11, 2.16 (3H, s×2), 2.67, 3.24 (1H, m×2), 3.00—3.15 (1H, m), 3.22 (1H, dd, J=5.8, 3.6 Hz), 3.40, 3.75 (1H, d× 2, J=15.2 Hz), 3.96, 4.85 (1H, br d×2, J=13 Hz), 4.15—4.30 (1H, m), 4.27 (1H, dd, J=10.8, 3.6 Hz), 4.65—4.85 (2H, m), 5.28 (1H, d, J=10.5 Hz), 5.45 (1H, br d, J=17 Hz), 5.50, 6.09 (1H, br d×2, J=15 Hz), 5.90—6.05 (1H, m). IR (KBr): 1782, 1718, 1649 cm^{-1}. *Anal.* Calcd for $C_{23}H_{36}N_2O_5Si$: C, 61.58; H, 8.09; N, 6.24. Found: C, 61.49; H, 8.24; N, 6.13. MS (FAB) m/z: 449 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[2-(Allyloxycarbonylamino)acetyl]-10-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10b) A solution of **3**, freshly prepared from **2** (250 mg, 4.93×10^{-4} mol) in a manner similar to that described above, in CH_2Cl_2 (0.5 ml) was added to a mixture of 1,1′-carbonyldiimidazole (CDI, 101 mg, 6.20×10^{-4} mol) and *N*-(allyloxycarbonyl)glycine[13d] (98.2 mg, 6.17×10^{-4} mol) in CH_2Cl_2 (3 ml) at 0 °C. After being stirred at the same temperature for 15 min, the mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH_4Cl, a saturated aqueous solution of $NaHCO_3$, and then brine. The organic layer was dried and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel (8 g) using a mixture of EtOAc and hexane (1 : 1) as eluent to give **10b** (138 mg, 51%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.21 (3H, d, J=6.0 Hz), 1.45—1.70 (1H, m), 1.80—2.00 (1H, m), 2.70—3.30 (2H, m), 3.21 (1H, dd, J=5.7, 3.7 Hz), 3.46, 3.73 (1H, br d×2, J=15.0 Hz), 3.87, 4.80 (1H, br d×2, J=13 Hz), 3.90—4.20 (2H, m), 4.21 (1H, m), 4.28 (1H, dd, J=11.0, 3.7 Hz), 4.59 (2H, br d, J=5.3 Hz), 4.70—4.90 (2H, m), 5.15—5.50 (4H, m), 5.47, 6.10 (1H, br d×2, J=15 Hz), 5.62, 5.78 (1H, m×2), 5.75—6.15 (2H, m). IR (KBr): 3343, 1782, 1724, 1657 cm^{-1}. MS (FAB) m/z: 548 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[3-(Allyloxycarbonylamino)propionyl]-10-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (10c) A solution of **3**, freshly prepared from **2** (370 mg, 7.30×10^{-4} mol) in a manner similar to that described above, in CH_2Cl_2 (2 ml) was added to a mixture of CDI (178 mg, 1.10×10^{-3} mol) and 3-(allyloxycarbonylamino)propionic acid (190 mg, 1.10×10^{-3} mol) in CH_2Cl_2 (1.5 ml) at 0 °C. After being stirred at the same temperature for 20 min, the mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH_4Cl, a saturated aqueous solution of $NaHCO_3$, and then brine. The organic layer was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (12 g) using a mixture of EtOAc and hexane (1 : 1) as eluent to give **10c** (227 mg, 55%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.21 (3H, d, J=6.1 Hz), 1.45—1.70 (1H, m), 1.75—2.00 (1H, m), 2.40—3.25 (5H, m), 3.38, 3.70 (1H, br d×2, J=14 Hz), 3.40—3.55 (2H, m), 3.97, 4.82 (1H, br d, J=14 Hz), 4.15—4.30 (2H, m), 4.54 (2H, br d, J=5.4 Hz), 4.65—4.85 (2H, m), 5.15—5.65 (5H, m), 5.48, 6.11 (1H, br d×2, J=14 Hz), 5.80—6.05 (2H, m). IR (KBr): 3338, 1782, 1721, 1648 cm^{-1}. MS (FAB) m/z: 562 $(M+H)^+$.

Allyl (8*S*,9*R*,11*S*)-5-[2-[(*N*-Allyloxycarbonyl-*N*-methyl)amino]acetyl]-10-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10d) A solution of **3**, freshly prepared from **2** (2.04 g, 4.02×10^{-3} mol) in a manner similar to that described above, in DMF (8 ml) was added to a mixture of CDI (899 mg, 5.54×10^{-3} mol) and *N*-allyloxycarbonylsarcosine (870 mg, 5.02×10^{-3} mol) in DMF (17 ml) at 0 °C. After being stirred at room temperature for 6 h, the mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH_4Cl, a saturated aqueous solution of $NaHCO_3$, and then brine. The

organic layer was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (80 g) using a mixture of EtOAc and hexane (3 : 2) as eluent to give **10d** (1.60 g, 71%) as a pale yellow viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.89 (9H, s), 1.22 (3H, d, J=6.2 Hz), 1.50—1.70 (1H, m), 1.80—1.95 (1H, m), 2.65—3.30 (1H, m), 2.99, 3.00 (3H, s×2), 3.08 (1H, m), 3.22 (1H, m), 3.48, 3.72 (1H, br d×2, J=14 Hz), 3.80—4.90 (8H, m), 4.26 (1H, dd, J=10.6, 3.4 Hz), 5.10—6.10 (7H, m). IR (KBr): 3338, 1782, 1721, 1648 cm^{-1}. MS (FAB) m/z: 562 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[3-(*tert*-Butoxycarbonylamino)propionyl]-10-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (10e) A solution of **3**, freshly prepared from **2** (600 mg, 1.18×10^{-3} mol) in a manner similar to that described above, in DMF (4 ml) was added to a mixture of CDI (288 mg, 1.78×10^{-3} mol) and 3-(*tert*-butoxycarbonylamino)propionic acid[16] (336 mg, 1.78×10^{-3} mol) in DMF (2 ml) at 0 °C. After being stirred at the same temperature for 3 h, the mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH_4Cl, a saturated aqueous solution of $NaHCO_3$, and then brine. The organic layer was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (15 g) using a mixture of EtOAc and hexane (1 : 1) as eluent to give **10e** (591 mg, 86%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.22 (3H, d, J=6.3 Hz), 1.43 (9H, s), 1.45—1.70 (1H, m), 1.75—2.00 (1H, m), 2.40—3.25 (5H, m), 3.30—3.50 (2H, m), 3.38, 3.70 (1H, br d×2, J=14 Hz), 3.97, 4.82 (1H, br d×2, J=14 Hz), 4.15—4.30 (2H, m), 4.65—4.90 (2H, m), 5.20—5.55 (3H, m), 5.48 and 6.11 (1H, br d, J=14 Hz), 5.85—6.05 (1H, m). IR (KBr): 3361, 1783, 1714, 1647 cm^{-1}. MS (FAB) m/z: 578 $(M+H)^+$.

***N*,*N*′-Bis(allyloxycarbonyl)amidinopyrazole** This reagent was prepared following the literature procedure for the preparation of *N*,*N*′-bis(tert-butoxycarbonyl)amidinopyrazole.[13] To a suspension of amidinopyrazole hydochloride (6.00 g, 40.9 mmol) in DMF–THF (1 : 1, 60 ml) were added allyl chloroformate (4.55 ml, 43 mmol) and Et_3N (11.8 ml, 85 mmol) at 0 °C. After being stirred at room temperature for 3 h, the mixture was diluted with EtOAc (100 ml) and washed with water, a saturated aqueous solution of NH_4Cl and brine, successively. The organic layer was dried and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel (200 g) using a mixture of EtOAc and hexane (1 : 1) as eluent to give *N*-(allyloxycarbonyl)amidinopyrazole (7.02 g, 90%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 4.69 (2H, d, J=6 Hz), 5.27 (1H, d, J=10 Hz), 5.38 (1H, d, J=17 Hz), 6.03 (1H, ddt, J= 17, 10, 6 Hz), 6.43 (1H, m), 7.71 (1H, br s), 7.60—7.90 (1H, m), 8.47 (1H, d, J=3 Hz), 9.07 (1H, m). To a solution of this oil (4.60 g, 27.7 mmol) in THF (100 ml) was added sodium hydride (55% mineral oil dispersion, 2.55 g, 58.4 mmol, washed with hexane) at 0 °C. After being stirred at room temperature for 30 min, a solution of diallyl dicarbonate (5.6 g, 30 mmol) in THF (10 ml) was added at 0 °C and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc. The extract was washed with brine, dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (350 g) using a mixture of EtOAc and hexane (2 : 1) as eluent to give *N*,*N*′-bis(allyloxycarbonyl)amidinopyrazole (5.4 g, 70%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 4.65—4.75 (4H, m), 5.20—5.50 (4H, m), 5.85—6.15 (2H, m), 6.47 (1H, dd, J=3, 1 Hz), 7.67 (1H, m), 8.32 (1H, d, J=3 Hz), 9.31 (1H, br s).

Allyl (8*S*,9*R*,10*S*)-5-[3-[[*N*,*N*′-Bis(allyloxycarbonyl)amidino]amino]-propionyl]-10-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10f) To a solution of **10e** (485 mg, 8.39×10^{-4} mol) and 2,6-lutidine (294 μl, 2.52×10^{-3} mol) in CH_2Cl_2 (6 ml) was added TMSOTf (352 μl, 1.82×10^{-3} mol) at 0 °C. After being stirred at room temperature for 15 min, the mixture was quenched with a saturated aqueous solution of $NaHCO_3$, and extracted with EtOAc. The extract was washed with brine, dried and concentrated under reduced pressure. The residue was dissolved in THF (3 ml), and a solution of *N*,*N*′-bis(allyloxycarbonyl)amidinopyrazole (234 mg, 8.40×10^{-4} mol) in THF (2 ml) was added at room temperature. After being stirred at the same temperature for 15 h, the mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH_4Cl and brine. The organic layer was dried and concentrated under reduced pressure. The crude product was subjected to HPLC using $CHCl_3$ as eluent to give **10f** (203 mg, 35%) as a pale yellow viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.21 (3H, d, J=6.3 Hz), 1.45—1.65 (1H, m), 1.75—2.00 (1H, m), 2.50—3.25 (3H, m), 3.07 (1H, m), 3.21 (1H, dd, J=5.8, 3.6 Hz), 3.41, 3.69 (1H, br d×2, J=14 Hz), 3.70—3.85 (2H, m), 3.98, 4.89 (1H, br d×2, J=14 Hz), 4.15—4.25 (1H, m), 4.27 (1H, dd, J=10.6, 3.6 Hz), 4.60 (2H, d, J=5.8 Hz), 4.65 (2H, d, J=5.8 Hz), 4.65—4.80 (2H, m), 5.20—5.50 (6H, m), 5.46, 6.08 (1H, br d×2, J=14 Hz), 5.80—6.10 (3H, m), 8.88, 9.00 (1H, br t×2, J=6 Hz), 11.65, 11.69 (1H, br s×2). IR (KBr): 3342, 1784, 1733, 1641, 1562 cm^{-1}. MS (FAB) m/z: 688 $(M+H)^+$.

Allyl (8*S*,9*R*,11*S*)-10-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-11-oxo-5-(3-pyridylcarbonyl)-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10g) To a solution of **3**, freshly prepared from **2** (260 mg, 5.13×10^{-4} mol) in a manner similar to that described above, in CH_2Cl_2 (3 ml) was added Et_3N (179 μl, 1.28×10^{-3} mol) and nicotinoyl chloride hydrochloride (114 mg, 6.40×10^{-4} mol) at 0 °C. After being stirred at the same temperature for 30 min, the mixture was poured into phosphate buffer (pH 7.4, 10 ml) and extracted with EtOAc. The extract was washed with brine, dried and concentrated under reduced pressure to give an oily residue, which was purified by column chromatography on silica gel (8 g) using a mixture of EtOAc and methanol (1 : 0 to 9 : 1) as eluent to afford **10g** (207 mg, 79%) as a pale yellow viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.23 (3H, d, J=6.2 Hz), 1.60—1.80 (1H, m), 1.80—2.00 (1H, m), 2.80—3.30 (1H, m), 3.13 (1H, td, J=11.0, 5.0 Hz), 3.27 (1H, dd, J=5.4, 3.8 Hz), 3.50—4.10 (1H, m), 4.23 (1H, m), 4.28 (1H, dd, J=10.8, 3.8 Hz), 4.30—6.20 (7H, m), 7.36 and 7.38 (1H, d×2, J=8.0 Hz), 7.76, 7.77 (1H, dd×2, J=8.0, 2.0 Hz), 8.67, 8.68 (1H, s×2), 8.69, 8.70 (1H, d×2, J=2,0 Hz). IR (KBr): 1782, 1724, 1640 cm^{-1}. MS (FAB) m/z: 512 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-10-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-11-oxo-5-(4-pyridylcarbonyl)-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10h) A solution of **3**, freshly prepared from **2** (501 mg, 9.89×10^{-4} mol) in a manner similar to that described above, in DMF (0.5 ml) was added to a mixture of CDI (192 mg, 1.18×10^{-3} mol) and isonicotinic acid (152 mg, 1.24×10^{-3} mol) in DMF (4 ml) at 0 °C. After being stirred at the same temperature for 35 min, the mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH_4Cl, a saturated aqueous solution of $NaHCO_3$, and then brine. The organic layer was dried and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel (15 g) using a mixture of EtOAc and methanol (1 : 0 to 9 : 1) as eluent to give **10h** (350 mg, 69%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.23 (3H, d, J=6.2 Hz), 1.50—2.10 (2H, m), 2.80—3.20 (1H, m), 3.13 (1H, td, J=12.0, 5.0 Hz), 3.27 (1H, m), 3.40—4.00 (1H, m), 4.23 (1H, m), 4.28 (1H, dd, J=10.8, 3.6 Hz), 4.30—6.30 (7H, m), 7.28 (2H, d, J=5.8 Hz), 8.70 (2H, d, J=5.8 Hz). IR (KBr): 1783, 1721, 1642 cm^{-1}. MS (FAB) m/z: 512 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-Allyloxycarbonyl-10-[(*R*)-1-(hydroxy)ethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10i) To a solution of **2** (250 mg, 4.93×10^{-4} mol) and 2,6-lutidine (86 μl, 7.4×10^{-4} mol) in CH_2Cl_2 (2.5 ml) was added TMSOTf (118 μl, 6.11×10^{-4} mol) at 0 °C. After being stirred at room temperature for 15 min, the mixture was cooled at 0 °C, and a saturated aqueous solution of $NaHCO_3$ (25 μl) was added. Stirring was continued for 15 min, then, Et_3N (86 μl, 6.2×10^{-4} mol) and allyl chloroformate (65 μl, 6.2×10^{-4} mol) were added at 0 °C, and the whole was stirred for 10 min. The mixture was diluted with EtOAc, washed with a saturated aqueous solution of NH_4Cl, a saturated aqueous solution of $NaHCO_3$, and then brine. The organic layer was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (8 g) using a mixture of EtOAc and hexane (1 : 1) as eluent to give **10i** (198.9 mg, 82%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.22 (3H, d, J=6.3 Hz), 1.60 (1H, dq, J=13.0, 4.0 Hz), 1.80—1.90 (1H, m), 2.85—3.10 (2H, m), 3.22 (1H, dd, J=6.1, 3.7 Hz), 3.58 (1H, br d, J=15.0 Hz), 4.15—4.30 (1H, m), 4.25 (1H, d, J=11.0, 3.7 Hz), 4.30—4.50 (1H, m), 4.60 (2H, d, J=5.5 Hz), 4.65—4.85 (2H, m), 5.20—5.50 (4H, m), 5.72 (1H, d, J=15 Hz), 5.85—6.05 (2H, m). IR ($CHCl_3$): 1780, 1699, 1650 cm^{-1}. MS (FAB) m/z: 491 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-10-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-5-methyl-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10j) To a solution of **3**, freshly prepared from **2** (300 mg, 5.92×10^{-4} mol) in a manner similar to that described above, in DMF (2 ml) were added Et_3N (420 μl, 3.0×10^{-3} mol) and a solution of iodomethane (170 mg, 1.20×10^{-3} mol) in DMF (0.5 ml) at 0 °C. After being stirred at the same temperature for 1 h, the mixture was diluted with EtOAc and washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel (25 g) using a mixture of EtOAc and methanol (95 : 5) as eluent to give **10j** (97.8 mg, 39%) as a pale yellow viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.88 (9H, s), 1.23 (3H, d, J=6.3 Hz), 1.75—1.85 (2H, m), 2.15—2.35 (1H, m), 2.37 (3H, s), 2.71 (1H, d, J=12.3 Hz), 2.75—2.90 (1H, m), 2.99 (1H, br d, J=12 Hz), 3.24 (1H, dd, J=6.3, 3.6 Hz), 4.10—4.25 (1H, m), 4.21 (1H, dd, J=8.3, 3.6 Hz), 4.39 (1H, d, J=12.3 Hz),

4.60—4.85 (2H, m), 5.25 (1H, dd, J=10.3, 1.2 Hz), 5.42 (1H, dd, J=17.3, 1.7 Hz), 5.93 (1H, ddt, J=17.3, 10.7, 5.3 Hz). IR (KBr): 1783, 1720, 1648 cm^{-1}. MS (FAB) m/z: 421 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-10-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-5-(carbamoyl)methyl-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10k) To a solution of **3**, freshly prepared from **2** (506 mg, 1.00×10^{-3} mol) in a manner similar to that described above, in DMF (5 ml) were added K_2CO_3 (138 mg, 1.00×10^{-3} mol) and 2-iodoacetamide (925 mg, 5.00×10^{-3} mol) at room temperature. After being stirred at the same temperature for 1 h, the mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH_4Cl and brine. The organic layer was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (20 g) using a mixture of EtOAc and methanol (1 : 0 to 10 : 1) as eluent to give **10k** (416 mg, 90%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.24 (3H, d, J=6.2 Hz), 1.60—1.90 (2H, m), 2.50 (1H, td, J=11.6, 2.7 Hz), 2.80—3.00 (1H, dd, J=8.3, 3.6 Hz), 2.92 (1H, d, J=12.1 Hz), 3.04 (1H, br d, J=12 Hz), 3.10 (2H, s), 3.23 (1H, dd, J=6.2, 3.5 Hz), 4.10—4.30 (2H, m), 4.45 (1H, d, J=12.1 Hz), 4.60—4.90 (2H, m), 5.26 (1H, dd, J=10.5, 1.2 Hz), 5.42 (1H, dd, J=17.2, 1.4 Hz), 5.70 (1H, br s), 5.95 (1H, ddt, J=17.2, 10.5, 5.4 Hz), 6.89 (1H, br s). IR (KBr): 3454, 3283, 1780, 1716, 1667 cm^{-1}. MS (FAB) m/z: 464 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-10-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-5-carbamoyl-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10l) To a solution of **3**, freshly prepared from **2** (250 mg, 4.93×10^{-4} mol) in a manner similar to that described above, in CH_2Cl_2 (3 ml) was added trimethylsilyl isocyanate (117 μl, 8.64×10^{-4} mol) at 0 °C. After being stirred at the same temperature for 1 h, the mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH_4Cl. The organic layer was dried and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel (8 g) using a mixture of EtOAc and methanol (1 : 0 to 95 : 5) as eluent and then HPLC using $CHCl_3$ as eluent to give **10l** (135.5 mg, 61%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.21 (3H, d, J=6.4 Hz), 1.61 (1H, qd, J=12, 4 Hz), 1.75—1.90 (1H, m), 2.85 (1H, ddd, J=14, 12, 2 Hz), 3.08 (1H, td, J=11.5, 5.5 Hz), 3.22 (1H, dd, J=5.9, 3.8 Hz), 3.67 (1H, br d, J=15 Hz), 4.21 (1H, m), 4.27 (1H, dd, J=10.7, 3.8 Hz), 4.52 (1H, br d, J=14 Hz), 4.60—4.90 (2H, m), 4.92 (2H, br s), 5.10 (1H, br d, J=15 Hz), 5.29 (1H, dd, J=10.5, 1.3 Hz), 5.45 (1H, br d, J=17.2Hz), 5.96 (1H, ddt, J=17.2, 10.5, 5.3 Hz). IR (KBr): 3453, 3347, 3215, 1772, 1718, 1651, 1602 cm^{-1}. MS (FAB) m/z: 450 $(M+H)^+$.

***N*-(Allyloxycarbonyl)guanidine** To a solution of guanidine hydrochloride (2.00 g, 20.9 mmol) in a mixture of H_2O and THF (3 : 1, 40 ml) were added 2 N NaOH (21 ml) and a solution of allyl chloroformate (2.53 g, 21.0 mmol) in THF (10 ml) at room temperature. After being stirred for 1 h, the mixture was concentrated under reduced pressure to *ca.* 40 ml. The resultant precipitates that emerged were sparingly soluble in water and removed by filtration. The filtrate was further concentrated under reduced pressure to *ca.* 5 ml. The resultant solids which were water-soluble were collected by filtration and washed with cold water to give *N*-(allyloxycarbonyl)guanidine (682 mg, 23%) as colorless crystals, mp 137—139 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.39 (2H, br d, J=5 Hz), 5.11 (1H, br d, J=10 Hz), 5.22 (1H, br d, J=17 Hz), 5.90 (1H, ddt, J=17, 10, 5 Hz) 6.50—7.50 (4H, m). IR (KBr): 3444, 3401, 3333, 3045, 1650, 1627, 1592, 1527 cm^{-1}. MS (EI) m/z: 143 $(M)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[[N^{ω}-(Allyloxycarbonyl)guanidino]carbonyl]-10-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10m) A solution of **3**, freshly prepared from **2** (450 mg, 8.88×10^{-4} mol) in a manner similar to that described above, and *N*,*N*′-diisopropylethylamine (160 μl, 9.19×10^{-4} mol) in CH_2Cl_2 (5 ml) were added to a solution of triphosgene (90.0 mg, 3.03×10^{-4} mol) in CH_2Cl_2 (1 ml) at 0 °C. After being stirred at the same temperature for 30 min, DMAP (108 mg, 8.84×10^{-4} mol) and (allyloxycarbonyl)guanidine (160 mg, 1.12×10^{-3} mol) were added and the mixture was stirred at 0 °C for 2 h. The mixture was diluted with EtOAc and washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel (15 g) using a mixture of EtOAc and hexane (2 : 3) as eluent to give **10m** (187 mg, 31%) as a pale yellow viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.88 (9H, s), 1.22 (3H, d, J=6.1 Hz), 1.40—1.70 (1H, m), 1.75—1.90 (1H, m), 2.75—3.10 (2H, m), 3.21 (1H, dd, J=6.1, 3.7 Hz), 3.52 (1H, br d, J=15 Hz), 4.15—4.25 (1H, m), 4.23 (1H, dd, J=10.7, 3.7 Hz), 4.50—4.80 (2H, m), 4.65 (2H, d, J=5.8 Hz), 4.76 (2H, d, J=5.4 Hz), 5.25—5.35 (3H, m), 5.36 (1H, br d, J=17.2 Hz), 5.47 (1H, dd, J=17.2, 1.2 Hz), 5.80—6.20 (3H, m), 7.70—8.10 (1H, m). IR (KBr): 3408, 1783, 1729, 1651 cm^{-1}. MS (FAB) m/z: 576 $(M+H)^+$.

3-Amino-1-(allyloxycarbonyl)pyrrolidine Hydrogen Chloride To a solution of 3-(*tert*-butoxycarbonylamino)pyrrolidine (1.86 g, 10.0 mmol) in CH_2Cl_2 (20 ml) was added Et_3N (1.46 ml, 10.5 mmol) and allyl chloroformate (1.11 ml, 10.5 mmol) at 0 °C. After being stirred at the same temperature for 1 h, a saturated aqueous solution of NH_4Cl was added and extracted with EtOAc. The extract was washed with brine, dried and concentrated under reduced pressure. The residue was dissolved in EtOAc (10 ml) and treated with 4 N HCl in EtOAc (5 ml) at room temperature. A pale yellow oil that emerged was separated by decantation and dried under reduced pressure. 3-Amino-1-(allyloxycarbonyl)pyrrolidine hydrogen chloride (2.08 g, *ca.* 100%) thus obtained as a pale yellow oil was used for the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 2.20—2.40 (2H, m), 3.40—4.15 (5H, m), 4.58 (2H, m), 5.10 (1H, d, J=10.2 Hz), 5.31 (1H, d, J=17.1 Hz), 5.91 (1H, m), 8.55 (3H, br s).

Allyl (8*S*,9*R*,10*S*)-5-[[1-(Allyloxycarbonyl)pyrrolidin-3-yl]carbamoyl]-10-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo-[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10n) To a solution of **3**, freshly prepared from **2** (100 mg, 1.97×10^{-4} mol) in a manner similar to that described above, in CH_2Cl_2 (1 ml) was added a solution of 3-isocyanato-1-(allyloxycarbonyl)pyrrolidine, which was prepared from 3-amino-1-(allyloxycarbonyl)pyrrolidine hydrogen chloride (42 mg, 2.0×10^{-4} mol) and triphosgene (20 mg, 6.7×10^{-5} mol) in the presence of ethyldiisopropylamine (90 μl, 5.0×10^{-4} mol) in CH_2Cl_2 (2 ml), at room temperature. After being stirred at the same temperature for 30 min, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with EtOAc. The extract was washed with a saturated aqueous solution of NH_4Cl and brine, dried and concentrated under reduced pressure. After removal of solvent under reduced pressure, the residue was subjected to column chromatography on silica gel (10 g) using EtOAc as eluent to give **10n** (90.4 mg, 76%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.88 (9H, s), 1.21 (3H, d, J=6.2 Hz), 1.55—1.95 (3H, m), 2.00—2.20 (1H, m), 2.86 (1H, br t, J=13 Hz), 3.00—3.40 (2H, m), 3.19 (1H, dd, J=5.8, 3.5 Hz), 3.50—3.75 (3H, m), 3.61 (1H, d, J=15.4 Hz), 4.10—4.40 (3H, m), 4.45—4.65 (3H, m), 4.65—5.10 (3H, m), 5.15—5.50 (4H, m), 5.70—6.05 (3H, m). IR (KBr): 3370, 1782, 1704 1649 cm^{-1}. MS (FAB) m/z: 603 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-10-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-5-(*N*-methyl)thiocarbamoyl-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10o) To a solution of **3**, freshly prepared from **2** (255 mg, 5.03×10^{-4} mol) in a manner similar to that described above, in CH_2Cl_2 (2 ml) was added methyl isothiocyanate (73 mg, 1.0×10^{-3} mol) at room temperature. After being stirred at the same temperature for 1 h. The mixture was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (10 g) using a mixture of EtOAc and hexane (2 : 1) as eluent to give **10o** (196 mg, 81%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.88 (9H, s), 1.20 (3H, d, J=6.2 Hz), 1.72 (1H, qd, J=12, 4 Hz), 1.80—1.90 (1H, m), 3.12 (3H, d, J=5.3 Hz), 3.10—3.30 (2H, m), 3.24 (1H, dd, J=5.7, 3.7 Hz), 3.75 (1H, d, J=15.0 Hz), 4.20 (1H, m), 4.30 (1H, dd, J=10.7, 3.7 Hz), 4.70—4.90 (2H, m), 5.27 (1H, br d, J=15 Hz), 5.30 (1H, d, J=10.7 Hz), 5.46 (1H, dd, J=17.2, 1.3 Hz), 5.58 (1H, br d, J=12 Hz), 5.95 (1H, ddt, J=17.2, 10.7, 5.4 Hz), 6.85—7.00 (1H, m). IR (KBr): 3362, 1781, 1718, 1648 cm^{-1}. MS (FAB) m/z: 480 $(M+H)^+$.

1-(Allyloxycarbonyl)pyrrolidin-3-yl Isothiocyanate To a solution 3-amino-1-(allyloxycarbonyl)pyrrolidine (870 mg, 5.1 mmol), which was provided by neutralization of 3-amino-1-(allyloxycarbonyl)pyrrolidine hydrogen chloride by treatment with an aqueous solution of $NaHCO_3$, in CH_2Cl_2 (8 ml) was added 1,1′-thiocarbonyldiimidazole (1.00 g, 5.61 mmol) at −78 °C. After being stirred at 0 °C for 3 h, phosphate buffer (pH 7, 20 ml) was added and the mixture was extracted with EtOAc. The extract was washed with brine, dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (30 g) using a mixture of EtOAc and hexane (1 : 1) as eluent to give 1-(allyloxycarbonyl)pyrrolidin-3-yl isothiocyanate (896 mg, 83%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.19 (2H, m), 3.50—3.75 (4H, m), 4.31 (1H, m), 4.62 (2H, d, J=5.5 Hz), 5.23 (1H, d, J=10.3 Hz), 5.32 (1H, d, J=17.2 Hz), 5.95 (1H, m). IR (CH_3Cl): 2090, 1700 cm^{-1}. MS (EI) m/z: 212 $(M)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[[*N*-(Allyloxycarbonyl)pyrrolidin-3-yl]thiocarbamoyl]-10-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10p) To a solution of **3**, freshly prepared from **2** (300 mg, 5.92×10^{-4} mol) in a manner similar to that described above, in CH_2Cl_2 (2 ml) was added *N*-(allyloxycarbonyl)pyrrolidin-3-yl isothiocyanate (188 mg, 8.88×10^{-4} mol) at room temperature. After being stirred for 1 h, the mixture was concentrated under reduced pres-

sure. The residue was subjected to column chromatography on silica gel (10 g) using a mixture of EtOAc and hexane (1 : 1) as eluent and then HPLC using $CHCl_3$ as eluent to give **10p** (280 mg, 77%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.88 (9H, s), 1.20 (3H, d, J=6.1 Hz), 1.72 (1H, qd, J=12, 4 Hz), 1.80—2.35 (3H, m), 3.10—3.65 (5H, m), 3.24 (1H, dd, J=5.7, 3.7 Hz), 3.70—3.85 (1H, m), 3.74 (1H, d, J=14.8 Hz), 4.20 (1H, m), 4.30 (1H, m), 4.50—5.05 (5H, m), 5.15—5.55 (5H, m), 5.60 (1H, br d, J=14 Hz), 5.85—6.05 (2H, m), 7.09 (1H, m). IR (KBr): 3336, 1783, 1701, 1648, 1539 cm^{-1}. MS (FAB) m/z: 619 $(M+H)^+$.

***N*-(Allyloxycarbonyl)acetamidine hydrochloride** To a solution of acetamidine hydrochloride (10.4 g, 1.10×10^{-2} mol) in a mixture of 1 N NaOH (220 ml) and THF (100 ml) was added allyl chloroformate (11.6 ml, 1.10×10^{-2} mol) dropwise at 0 °C. After being stirred for 2 h at room temperature, the mixture was saturated with NaCl and extracted with EtOAc. The extract was washed with brine, dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (125 g) using a mixture of EtOAc and MeOH (4 : 1) as eluent to give *N*-(allyloxycarbonyl)acetamidine (11.4 g, 73%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, s), 4.60 (2H, d, J=5 Hz), 5.22 (1H, d, J=10 Hz), 5.35 (1H, d, J=17 Hz), 5.96 (1H, ddt, J=17, 10, 5 Hz), 6.22 (1H, m), 9.25 (1H, m). IR (KBr): 3367, 1777, 1578 cm^{-1}. MS (EI) m/z: 142 $(M)^+$. To a solution of this oil (5.0 g, 35 mmol) in EtOAc (40 ml) was added 4 N HCl in EtOAc (20 ml) at 0 °C. The solid that emerged was collected by filtration, and washed with EtOAc to afford *N*-(allyloxycarbonyl)acetamidine hydrochloride (5.54 g, 89%) as a colorless viscous oil. ^{1}H-NMR (D_2O) δ: 2.44 (3H, s), 4.83 (2H, d, J=6 Hz), 5.39 (2H, d, J=11 Hz), 5.46 (2H, d, J=17 Hz), 6.04 (1H, ddt, J=17, 11, 6 Hz). IR (KBr): 3325, 1754, 1742, 1560, 1550, 1255 cm^{-1}.

Allyl (8*S*,9*R*,10*S*)-5-[*N*-(Allyloxycarbonyl)acetimidoyl]-10-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10r) To a solution of **3**, freshly prepared from **2** (1.00 g, 1.97×10^{-3} mol) in a manner similar to that described above, in CH_2Cl_2 (10 ml) was added *N*-(allyloxycarbonyl)acetamidine hydrochloride (530 mg, 2.97×10^{-3} mol) at 0 °C. After being stirred at room temperature for 21 h, the mixture was diluted with EtOAc and washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel (40 g) using a mixture of EtOAc and hexane (2 : 3) as eluent to give **10r** (121 mg, 12%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.21 (3H, d, J=6.2 Hz), 1.50—1.80 (1H, m), 1.75—1.95 (1H, m), 2.29 (3H, s), 2.65—3.05 (1H, m), 3.10 (1H, td, J=12.2, 6.3 Hz), 3.24 (1H, dd, J=5.8, 3.6 Hz), 3.69 (1H, d, J=14.6 Hz), 4.22 (1H, m), 4.28 (1H, dd, J=10.8, 3.6 Hz), 4.61 (2H, d, J=5.8 Hz), 4.65—4.80 (2H, m), 4.80—5.20 (1H, m), 5.22 (1H, dd, J=10.2, 1.0 Hz), 5.27 (1H, dd, J=11.2, 1.0 Hz), 5.33 (1H, dd, J=17.3, 1.6 Hz), 5.44 (1H, dd, J=17.3, 1.7 Hz), 5.45—5.80 (1H, m), 5.85—6.10 (2H, m). IR (KBr): 1784, 1716, 1681, 1648, 1567 cm^{-1}. MS (FAB) m/z: 532 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[*N*,*N*′-Bis(allyloxycarbonyl)amidino]-10-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (10s) To a solution of **3**, freshly prepared from **2** (600 mg, 1.18×10^{-3} mol) in a manner similar to that described above, in THF (2 ml) was added a solution of *N*,*N*′-bis(allyloxycarbonyl)amidinopyrazole (334 mg, 1.20×10^{-3} mol) in THF (1 ml) at room temperature. After being stirred at the same temperature for 1 h, the mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH_4Cl and brine. The organic layer was dried and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel (20 g) using a mixture of EtOAc and hexane (1 : 2) as eluent and then HPLC using $CHCl_3$ as eluent to give **10s** (440 mg, 60%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.88 (9H, s), 1.21 (3H, d, J=6.2 Hz), 1.75—2.00 (2H, m), 3.05—3.20 (2H, m), 3.26 (1H, dd, J=6.0, 3.7 Hz), 3.87 (1H, br d, J=15.3 Hz), 4.21 (1H, m), 4.27 (1H, dd, J=10.9, 3.7 Hz), 4.50—4.80 (7H, m), 5.20—5.60 (7H, m), 5.85—6.10 (3H, m), 10.5 (1H, br s). IR (KBr): 3274, 1785, 1757, 1726, 1640, 1610 cm^{-1}. MS (FAB) m/z: 617 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-Acetyl-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11a) A mixture of **10a** (192 mg, 4.28×10^{-4} mol), ammonium hydrogen fluoride ($NH_4F\cdot HF$, 74 mg, 1.3×10^{-3} mol), DMF (1 ml) and *N*-methylpyrrolidinone (NMP, 1 ml) was stirred at room temperature for 64 h. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (8 g) using a mixture of EtOAc and methanol (1 : 0 to 9 : 1) as eluent and then HPLC using $CHCl_3$ as eluent to give **11a** (41.0 mg, 29%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.3 Hz), 1.45—1.70 (1H, m), 1.85—2.20 (2H, m), 2.11, 2.16 (3H, s×2), 2.60—3.30 (2H, m), 3.27 (1H, dd, J=6.4, 3.6 Hz), 3.40, 3.77 (1H, d×2, J=15.2 Hz), 3.97, 4.85 (1H, br d×2, J=14 Hz), 4.15—4.35 (1H, m), 4.33 (1H, dd, J=10.7, 3.6 Hz), 4.65—4.90 (2H, m), 5.30 (1H, d, J=10.5 Hz), 5.45 (1H, br d, J=16 Hz), 5.50, 6.08 (1H, br d×2, J=14 Hz), 5.90—6.05 (1H, m). IR (KBr): 3379, 1780, 1719, 1645, 1627 cm^{-1}. MS (FAB) m/z: 335 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[2-(Allyloxycarbonylamino)acetyl]-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11b) A mixture of **10b** (200 mg, 3.65×10^{-4} mol), ammonium hydrogen fluoride ($NH_4F\cdot HF$, 31.4 mg, 5.50×10^{-4} mol), DMF (1 ml) and NMP (1 ml) was stirred at room temperature for 7 d. The mixture was quenched with an aqueous solution of $NaHCO_3$, saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (8 g) using a mixture of EtOAc and methanol (97 : 3 to 90 : 10) as eluent to give **11b** (97.7 mg, 62%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.4 Hz), 1.45—1.70 (1H, m), 1.82 (1H, d, J=4.8 Hz), 1.80—2.10 (1H, m), 2.70—3.30 (2H, m), 3.26 (1H, dd, J=6.3, 3.5 Hz), 3.47, 3.75 (1H, d×2, J=15.0 Hz), 3.88, 4.83 (1H, br d×2, J=13 Hz), 3.90—4.20 (2H, m), 4.25 (1H, m), 4.33 (1H, dd, J=10.7, 3.5 Hz), 4.59 (2H, br d, J=5.3 Hz), 4.70—4.90 (2H, m), 5.20—5.50 (4H, m), 5.38, 6.10 (1H, d×2, J=15 Hz), 5.61, 5.77 (1H, m×2), 5.85—6.10 (2H, m). IR (KBr): 3402, 1777, 1720, 1651 cm^{-1}. MS (FAB) m/z: 434 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[3-(Allyloxycarbonylamino)propionyl]-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11c) A mixture of **10c** (200 mg, 3.56×10^{-4} mol), $NH_4F\cdot HF$ (63 mg, 1.1×10^{-3} mol), DMF (1 ml) and NMP (1 ml) was stirred at room temperature for 72 h. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (8 g) using a mixture of EtOAc and methanol (95 : 5) as eluent and then HPLC using $CHCl_3$ as eluent to give **11c** (79.0 mg, 50%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.3 Hz), 1.45—1.70 (1H, m), 1.75—2.00 (1H, m), 2.10—2.30 (1H, m), 2.40—3.30 (4H, m), 3.27 (1H, dd, J=6.2, 3.5 Hz), 3.41, 3.71 (1H, br d×2, J=14.6 Hz), 3.40—3.55 (2H, m), 3.97, 4.82 (1H, br d×2, J=14 Hz), 4.20—4.30 (1H, m), 4.32 (1H, dd, J=10.7, 3.5 Hz), 4.55 (2H, br d, J=5.4 Hz), 4.65—4.85 (2H, m), 5.15—5.65 (5H, m), 5.48, 6.10 (1H, br d×2, J=14 Hz), 5.80—6.05 (2H, m). IR (KBr): 3393, 1779, 1717, 1636 cm^{-1}. MS (FAB) m/z: 448 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[2-[(*N*-Allyloxycarbonyl-*N*-methly)amino]acetyl]-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11d) A mixture of **10d** (563 mg, 1.00×10^{-3} mol), $NH_4F\cdot HF$ (167 mg, 2.92×10^{-3} mol), DMF (3 ml) and NMP (3 ml) was stirred at room temperature for 72 h. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (18 g) using a mixture of EtOAc and methanol (95 : 5) as eluent and then HPLC using $CHCl_3$ as eluent to give **11d** (262 mg, 59%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, d, J=6.4 Hz), 1.50—1.70 (1H, m), 1.71 (1H, d, J=4.8 Hz), 1.85—2.00 (1H, m), 2.65—3.30 (1H, m), 2.98, 3.00 (3H, s×2), 3.12 (1H, m), 3.27 (1H, m), 3.50, 3.74 (1H, br d×2, J=15 Hz), 3.85—4.90 (8H, m), 4.26 (1H, dd, J=10.5, 3.4 Hz), 5.10—6.10 (7H, m). IR (KBr): 3434, 1780, 1706, 1660, 1651 cm^{-1}. MS (FAB) m/z: 448 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[3-[[*N*,*N*′-Bis(allyloxycarbonyl)amidino]amino]-propionyl]-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (11f) A mixture of **10f** (182 mg, 2.56×10^{-4} mol), $NH_4F\cdot HF$ (45 mg, 7.9×10^{-4} mol), DMF (1 ml) and NMP (1 ml) was stirred at room temperature for 70 h. An aqueous solution of $NaHCO_3$ was added to the mixture and extracted with a mixture of EtOAc and CH_2Cl_2 (10 : 1). The extract was dried and concentrated under reduced pressure. The residue was subjected to HPLC using $CHCl_3$ as eluent to give **11f** (98.0 mg, 54%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.2 Hz), 1.45—1.65 (1H, m), 1.76 (1H, br d, J=3.9 Hz), 1.85—2.00 (1H, m), 2.55—3.25 (4H, m), 3.26 (1H, dd, J=6.3, 3.6 Hz), 3.43, 3.71 (1H, br d×2, J=14.6 Hz), 3.65—3.90 (2H, m), 4.01, 4.90 (1H, br d×2, J=14 Hz), 4.20—4.35 (1H, m), 4.32 (1H, dd, J=10.7, 3.6 Hz), 4.60 (2H, d, J=5.8 Hz), 4.66 (2H, d, J=5.8 Hz), 4.65—4.85 (2H, m), 5.20—5.50 (6H, m), 5.48, 6.09 (1H, br d×2, J=14 Hz), 5.80—6.10 (3H, m), 8.87, 8.99 (1H, br t×2, J=6 Hz), 11.64, 11.69 (1H, br s×2). IR (KBr): 3342, 1781, 1733, 1641, 1565 cm^{-1}. MS (FAB) m/z: 574 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[(*R*)-1-Hydroxyethyl]-11-oxo-5-(3-pyridylcarbonyl)-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11g) A mix-

ture of **10g** (200 mg, 5.13×10^{-4} mol), ammonium hydrogen fluoride ($NH_4F\cdot HF$, 45 mg, 7.9×10^{-4} mol), DMF (1 ml) and NMP (1 ml) was stirred at room temperature for 7 d. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (6 g) using a mixture of EtOAc and methanol (1 : 0 to 8 : 2) as eluent to give **11g** (85 mg, 54%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, d, J=6.2 Hz), 1.50—1.80 (1H, m), 1.90—2.40 (2H, m), 2.80—3.30 (1H, m), 3.19 (1H, td, J=11.0, 5.0 Hz), 3.31 (1H, dd, J=5.9, 3.7 Hz), 3.40—4.00 (1H, m), 4.26 (1H, m), 4.34 (1H, dd, J=10.8, 3.7 Hz), 4.40—6.30 (7H, m), 7.37, 7.39 (1H, d×2, J=8.0 Hz), 7.76, 7.77 (1H, dd×2, J=8.0, 2.0 Hz), 8.66, 8.67 (1H, s×2), 8.69, 8.70 (1H, d×2, J=2,0 Hz). IR (KBr): 3422, 1779, 1720, 1634 cm^{-1}. MS (FAB) *m/z*: 398 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-11-oxo-5-(4-pyridylcarbonyl)-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11h) A mixture of **10h** (350 mg, 6.84×10^{-4} mol), $NH_4F\cdot HF$ (195 mg, 3.42×10^{-3} mol), DMF (2 ml) and NMP (2 ml) was stirred at room temperature for 24 h. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (9 g) using a mixture of EtOAc and methanol (9 : 1) as eluent to give **11h** (48 mg, 18%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, J=6.4 Hz), 1.50—2.20 (3H, m), 2.80—3.20 (1H, m), 3.18 (1H, td, J=11.5, 5.0 Hz), 3.30 (1H, m), 3.40—4.00 (1H, m), 4.25 (1H, m), 4.33 (1H, dd, J=10.7, 3.5 Hz), 4.30—6.40 (7H, m), 7.28 (2H, d, J=5.8 Hz), 8.70 (2H, d, J=5.8 Hz).

Allyl (8*S*,9*R*,10*S*)-5-Allyloxycarbonyl-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11i) A mixture of **10i** (220 mg, 4.48×10^{-4} mol), ammonium hydrogen fluoride ($NH_4F\cdot HF$, 76.7 mg, 1.34×10^{-3} mol), DMF (1 ml) and NMP (1 ml) was stirred at room temperature for 3 d. The mixture was quenched with an aqueous solution of $NaHCO_3$, saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (8 g) using a mixture of ethyl acetate and hexane (2 : 1 to 1 : 0) as eluent to give **11i** (94.0 mg, 56%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, d, J=6.4 Hz), 1.60 (1H, dq, J=12.3, 4.1 Hz), 1.85—2.00 (1H, m), 1.90 (1H, d, J=4.7 Hz), 2.85—3.15 (2H, m), 3.27 (1H, dd, J=6.3, 3.5 Hz), 3.60 (1H, br d, J=14.8 Hz), 4.20—4.30 (1H, m), 4.30 (1H, dd, J=10.7, 3.5 Hz), 4.30—4.45 (1H, m), 4.60 (2H, d, J=5.6 Hz), 4.65—4.85 (2H, m), 5.20—5.50 (4H, m), 5.73 (1H, d, J=14.8 Hz), 5.85—6.05 (2H, m). IR (KBr): 3610, 1782, 1718, 1698, 165 cm^{-1}. MS (FAB) *m/z*: 377 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-5-methyl-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11j) A mixture of **10j** (110 mg, 2.62×10^{-4} mol), $NH_4F\cdot HF$ (45 mg, 7.85×10^{-4} mol), DMF (0.5 ml) and NMP (0.5 ml) was stirred at room temperature for 47 h. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (9 g) using a mixture of EtOAc and methanol (4 : 1) as eluent and then HPLC using $CHCl_3$ as eluent to give **11j** (31.0 mg, 39%) as a pale yellow viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, d, J=6.1 Hz), 1.65—1.90 (2H, m), 1.83 (1H, d, J=3.4 Hz), 2.15—2.35 (1H, m), 2.37 (3H, s), 2.72 (1H, d, J=12.2 Hz), 2.80—2.95 (1H, m), 3.00 (1H, br d, J=12 Hz), 3.29 (1H, dd, J=6.3, 3.6 Hz), 4.20—4.30 (1H, m), 4.26 (1H, dd, J=10.5, 3.6 Hz), 4.40 (1H, d, J=12.2 Hz), 4.60—4.90 (2H, m), 5.26 (1H, dd, J=10.6, 1.2 Hz), 5.42 (1H, dd, J=17.2, 1.3 Hz), 5.97 (1H, ddt, J=17.2, 10.6, 5.4 Hz).

Allyl (8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-5-(carbamoyl)methyl-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11k) A mixture of **10k** (215 mg, 4.64×10^{-4} mol), $NH_4F\cdot HF$ (106 mg, 1.85×10^{-3} mol), DMF (1 ml) and NMP (1 ml) was stirred at room temperature for 46 h. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to HPLC using $CHCl_3$ as eluent to give **11k** (39.0 mg, 24%) as a pale yellow viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, J=6.4 Hz), 1.60—2.00 (3H, m), 2.51 (1H, td, J=11.9, 2.4 Hz), 2.80—3.00 (1H, dd, J=8.3, 3.6 Hz), 2.94 (1H, d, J=12.0 Hz), 3.05 (1H, br d, J=12 Hz), 3.11 (2H, s), 3.28 (1H, dd, J=6.4, 3.5 Hz), 4.20—4.30 (1H, m),4.28 (1H, dd, J=10.6, 3.5 Hz), 4.46 (1H, d, J=12.0 Hz), 4.60—4.90 (2H, m), 5.28 (1H, dd, J=10.5, 1.1 Hz), 5.42 (1H, dd, J=16.2, 1.2 Hz), 5.50 (1H, br s), 5.96 (1H, ddt, J=16.2, 10.5, 5.6 Hz), 6.88 (1H, br s). IR (neat): 3435, 3342, 1775, 1718, 1674 cm^{-1}. MS (FAB) *m/z*: 350 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-Carbamoyl-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11l) A mixture of **10l** (115 mg, 2.56×10^{-4} mol), $NH_4F\cdot HF$ (44 mg, 7.7×10^{-4} mol), DMF (1 ml) and NMP (1 ml) was stirred at room temperature for 96 h. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (9 g) using a mixture of EtOAc and methanol (9 : 1) as eluent and then HPLC using $CHCl_3$ as eluent to give **11l** (44.3 mg, 52%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.2 Hz), 1.66 (1H, qd, J=12, 4 Hz), 1.80—1.95 (1H, m), 2.12 (1H br s), 2.86 (1H, ddd, J=14, 12, 2 Hz), m), 3.13 (1H, td, J=11.2, 5.4 Hz), 3.27 (1H, dd, J=6.4, 3.5 Hz), 3.69 (1H, br d, J=15 Hz), 4.15—4.30 (1H, m), 4.33 (1H, dd, J=10.6, 3.5 Hz), 4.52 (1H, br d, J=14 Hz), 4.60—4.90 (2H, m), 4.92 (2H, br s), 5.12 (1H, br d, J=15 Hz), 5.30 (1H, br d, J=11 Hz), 5.45 (1H, br d, J=17.2Hz), 5.96 (1H, ddt, J=17.2, 11.0, 5.5 Hz). IR (KBr): 3367, 1775, 1719, 1651, 1596 cm^{-1}. MS (FAB) *m/z*: 336 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[[*N*$^{\varpi}$-(Allyloxycarbonyl)guanidino]carbonyl]-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11m) A mixture of **10m** (195 mg, 2.56×10^{-4} mol), $NH_4F\cdot HF$ (58 mg, 1.0×10^{-3} mol), DMF (1 ml) and NMP (1 ml) was stirred at room temperature for 43 h. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (9 g) using a mixture of EtOAc and hexane (4 : 1) as eluent and then HPLC using $CHCl_3$ as eluent to give **11m** (48.0 mg, 41%) as a pale yellow viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.0 Hz), 1.40—1.70 (2H, m), 1.80—1.95 (1H, m), 2.70—3.15 (2H, m), 3.26 (1H, dd, J=6.0, 3.8 Hz), 3.53 (1H, br d, J=14 Hz), 4.20—4.30 (1H, m), 4.27 (1H, dd, J=10.4, 3.8 Hz), 4.50—4.80 (4H, m), 4.67 (2H, d, J=5.5 Hz), 5.25—5.35 (3H, m), 5.36 (1H, d, J=17.2 Hz), 5.47 (1H, dd, J=17.2, 1.2 Hz), 5.80—6.20 (3H, m), 7.70—8.10 (1H, m).

Allyl (8*S*,9*R*,10*S*)-5-[[1-(Allyloxycarbonyl)pyroridin-3-yl]carbamoyl]-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11n) A mixture of **10n** (235 mg, 3.90×10^{-4} mol), $NH_4F\cdot HF$ (68 mg, 1.2×10^{-3} mol), DMF (1.2 ml) and NMP (1.2 ml) was stirred at room temperature for 48 h. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (9 g) using a mixture of EtOAc and methanol (1 : 0 to 9 : 1) as eluent and then HPLC using $CHCl_3$ as eluent to give **11n** (45.2 mg, 24%) as a pale yellow viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.4 Hz), 1.50—1.95 (3H, m), 2.00—2.35 (2H, m), 2.86 (1H, br t, J=13 Hz), 3.00—3.35 (2H, m), 3.24 (1H, dd, J=6.5, 3.4 Hz), 3.40—3.80 (3H, m), 3.63 (1H, d, J=15.4 Hz), 4.10—4.35 (3H, m), 4.45—4.65 (3H, m), 4.65—5.10 (3H, m), 5.15—5.50 (4H, m), 5.70—6.05 (3H, m). IR (KBr): 3382, 1777, 1699 1647 cm^{-1}. MS (FAB) *m/z*: 459 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-5-(*N*-methyl)thiocarbamoyl-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11o) A mixture of **10o** (196 mg, 4.05×10^{-4} mol), $NH_4F\cdot HF$ (88 mg, 1.5×10^{-3} mol), DMF (1 ml) and NMP (1 ml) was stirred at room temperature for 30 h. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (9 g) using a mixture of EtOAc and methanol (1 : 0 to 95 : 5) as eluent and then HPLC using $CHCl_3$ as eluent to give **11o** (59.8 mg, 40%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=6.0 Hz), 1.64 (1H, br s), 1.65—1.80 (1H, m), 1.85—1.95 (1H, m), 3.12 (3H, d, J=4.3 Hz), 3.10—3.30 (2H, m), 3.29 (1H, dd, J=6.2, 3.7 Hz), 3.78 (1H, d, J=15.2 Hz), 4.24 (1H, m), 4.36 (1H, dd, J=10.6, 3.7 Hz), 4.70—4.90 (2H, m), 5.29 (1H, dd, J=15.2, 1.9 Hz), 5.32 (1H, br d, J=10 Hz), 5.46 (1H, dd, J=15.2, 1.2 Hz), 5.58 (1H, br d, J=12 Hz), 5.97 (1H, ddt, J=15.2, 10.1, 5.6 Hz), 6.85—7.00 (1H, m). IR (KBr): 3369, 1776, 1717, 1646 cm^{-1}. MS (FAB) *m/z*: 366 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[[1-(Allyloxycarbonyl)pyroridin-3-yl]thiocarbamoyl]-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (11p) A mixture of **10p** (250 mg, 4.05×10^{-4} mol), $NH_4F\cdot HF$ (89 mg, 1.6×10^{-3} mol), DMF (1.25 ml) and NMP (1.25 ml) was stirred at room temperature for 48 h. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (3 g)

using a mixture of EtOAc and methanol (9 : 1) as eluent and then HPLC using $CHCl_3$ as eluent to give **11p** (137.5 mg, 67%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=6.4 Hz), 1.65—2.35 (4H, m), 1.84 (1H, br d, J=4 Hz), 1.72 (1H, qd, J=12, 4 Hz), 3.10—3.65 (5H, m), 3.28 (1H, dd, J=6.3, 3.6 Hz), 3.70—3.85 (1H, m), 3.76 (1H, d, J=14.7 Hz), 4.23 (1H, m), 4.36 (1H, dd, J=10.5, 3.6 Hz), 4.50—5.05 (5H, m), 5.15—5.55 (5H, m), 5.60 (1H, br d, J=13 Hz), 5.85—6.05 (2H, m), 7.09 (1H, m). IR (KBr): 3338, 1781, 1697, 1648, 1539 cm^{-1}. MS (FAB) m/z: 505 $(M+H)^+$.

Allyl (8*S*,9*R*,10*S*)-5-[*N*-(Allyloxycarbonyl)acetimidoyl]-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11r) A mixture of **10r** (87.0 mg, 1.56×10^{-4} mol), NH_4F HF (27 mg, 4.68×10^{-4} mol), DMF (0.4 ml) and NMP (0.4 ml) was stirred at room temperature for 24 h. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (5 g) using a mixture of EtOAc and methanol (95 : 5) as eluent and then HPLC using $CHCl_3$ as eluent to give **11r** (16.0 mg, 27%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.4 Hz), 1.55—1.80 (2H, m), 1.85—2.00 (1H, m), 2.29 (3H, s), 2.70—3.00 (1H, m), 3.15 (1H, br td, J=12, 5Hz), 3.27 (1H, dd, J=6.3, 3.6 Hz), 3.71 (1H, d, J=14.9 Hz), 4.15—4.35 (1H, m), 4.33 (1H, dd, J=10.7, 3.6 Hz), 4.50—5.10 (3H, m), 4.61 (2H, d, J=5.9 Hz), 5.22 (1H, dd, J=10.5, 1.2 Hz), 5.29 (1H, dd, J=10.5, 1.2 Hz), 5.34 (1H, dd, J=17.3, 1.3 Hz), 5.44 (1H, dd, J=17.2, 1.3 Hz), 5.50—6.05 (3H, m).

Allyl (8*S*,9*R*,10*S*)-5-[*N*,*N*′-Bis(allyloxycarbonyl)amidino]-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (11s) A mixture of **10s** (410 mg, 6.65×10^{-4} mol), NH_4F HF (114 mg, 2.00×10^{-3} mol), DMF (2 ml) and NMP (2 ml) was stirred at room temperature for 70 h. An aqueous solution of $NaHCO_3$ was added and the mixture was saturated with NaCl and extracted with EtOAc. The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (9 g) using a mixture of EtOAc, hexane and methanol (3 : 1 : 0 to 15 : 5 : 2) as eluent and then HPLC using $CHCl_3$ as eluent to give **11s** (205 mg, 61%) as a colorless viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=6.4 Hz), 1.70—2.00 (2H, m), 1.98 (1H, d, J=4.8 Hz), 3.10—3.25 (2H, m), 3.31 (1H, dd, J=6.2, 3.7 Hz), 3.89 (1H, d, J=15.3 Hz), 4.20—4.30 (1H, m), 4.32 (1H, dd, J=10.7, 3.7 Hz), 4.40—4.85 (7H, m), 5.20—5.80 (7H, m), 5.85—6.10 (3H, m), 10.5 (1H, br s). IR (KBr): 3285, 1757, 1723, 1640, 1606 cm^{-1}. MS (FAB) m/z: 503 $(M+H)^+$.

Potassium (8*S*,9*R*,10*S*)-5-Acetyl-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (4a) To a suspension of **11a** (37.0 mg, 1.13×10^{-4} mol), Pd $(PPh_3)_4$ (2.5 mg) and PPh_3 (2.8 mg) in EtOAc (1 ml) was added 0.5 M EtOAc solution of potassium 2-ethylhexanoate (0.22 ml) at room temperature and stirred for 10 min. Pale yellow precipitates that emerged were collected by filtration and washed with EtOAc. The crude solid thus obtained was purified by column chromatography on Cosmosil 75C_{18}-PREP (10 ml) using water as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4a** (29.5 mg, 80%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.27 (3H, d, J=6.5 Hz), 1.45—1.70 (1H, m), 1.90—2.05 (1H, m), 2.14, 2.20 (3H, s×2), 2.87, 3.32 (1H, m×2), 3.15—3.30 (1H, m), 3.44 (1H, dd, J=5.7, 3.4 Hz), 3.45, 3.87 (1H, d×2, J=13.9 Hz), 4.07, 4.55 (1H, br d×2, J=14 Hz), 4.20—4.30 (1H, m), 4.28 (1H, dd, J=10.4, 3.4 Hz), 5.46, 5.83 (1H, br d×2, J=14 Hz). IR (KBr): 3378, 1758, 1604 cm^{-1}. MS (FAB) m/z: 333 $(M+H)^+$.

(8*S*,9*R*,10*S*)-5-Aminoacetyl-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid (4b) To a mixture of **11b** (45.0 mg, 1.04×10^{-4} mol), Pd$(PPh_3)_4$ (3 mg) and PPh_3 (3 mg) in a mixture of EtOAc and THF (1 : 1, 1.5 ml) was added dimedone (58 mg, 4.2×10^{-4} mol) at room temperature. After being stirred for 45 min, the precipitates that emerged were collected by filtration and washed with a mixture of THF and EtOAc. The crude solid thus obtained was subjected to column chromatography on Cosmosil 75C_{18}-PREP (20 ml) using water as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4b** (8.2 mg, 26%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.27 (3H, d, J=5.9 Hz), 1.40—1.70 (1H, m), 1.90—2.10 (1H, m), 2.85—3.35 (2H, m), 3.35—3.45 (1H, m), 3.53, 3.87 (1H, d×2, J=14.0Hz), 4.00—4.35 (4H, m), 4.03, 4.55 (1H, br d×2, J= 13 Hz), 5.25, 5.85 (1H, d×2, J=14.0 Hz). IR (KBr): 3420, 1757, 1655, 1592 cm^{-1}. MS (FAB) m/z: 310 $(M+H)^+$.

(8*S*,9*R*,10*S*)-5-(3-Aminopropionyl)-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid (4c) To a mixture of **11c** (70.0 mg, 1.56×10^{-4} mol) and bis(triphenylphosphine)palladium dichloride ($Pd(PPh_3)_2Cl_2$, 5.4 mg) in CH_2Cl_2 (1.5 ml) was added n-Bu_3SnH (168 μl, 6.24×10^{-4} mol) at 0 °C. After being stirred at room temperature for 15 min, hexane (5 ml) was added to the reaction mixture. Pale yellow precipitates that emerged were collected by filtration and washed with EtOAc. The crude solid thus obtained was purified by column chromatography on Cosmosil 75C_{18}-PREP (10 ml) using water as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4c** (31 mg, 61%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.27 (3H, d, J=6.3 Hz), 1.45—1.70 (1H, m), 1.90—2.05 (1H, m), 2.75—2.95 (2H, m), 3.00—3.15 (1H, m), 3.15—3.40 (3H, m), 3.42 (1H, dd, J=5.8, 3.3 Hz), 3.46, 3.85 (1H, d×2, J=14.2 Hz), 4.03, 4.58 (1H, br d×2, J=14 Hz), 4.20—4.30 (1H, m), 4.28 (1H, dd, J=10.4, 3.3 Hz), 5.43, 5.88 (1H, d×2, J=14.2 Hz). IR (KBr): 3378, 3235, 1763, 1624 cm^{-1}. MS (FAB) m/z: 324 $(M+H)^+$.

(8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-5-[2-(*N*-methylamino)acetyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid (4d) To a mixture of **11d** (70.0 mg, 1.56×10^{-4} mol) and $Pd(PPh_3)_2Cl_2$ (5.4 mg) in CH_2Cl_2 (1.5 ml) was added n-Bu_3SnH (168 μl, 6.24×10^{-4} mol) at 0 °C. After being stirred at room temperature for 15 min, hexane was added to the reaction mixture. Pale yellow precipitates that emerged were collected by filtration and washed with EtOAc. The crude solid thus obtained was purified by column chromatography on Cosmosil 75C_{18}-PREP (10 ml) using water as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4d** (31 mg, 61%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.30 (3H, d, J=6.3 Hz), 1.50—1.70 (1H, m), 1.95—2.10 (1H, m), 2.80, 2.81 (3H, s×2), 2.95—3.40 (1H, m), 3.30 (1H, br td, J=11, 5 Hz), 3.46 (1H, dd, J=5.6, 3.3 Hz), 3.56, 3.91 (1H, br d×2, J=14 Hz), 4.10, 4.58 (1H, br d×2, J=14 Hz), 4.10—4.40 (4H, m), 5.26, 5.88 (1H, br d×2, J=14 Hz). IR (KBr): 3380, 1760, 1653, 1597 cm^{-1}. MS (FAB) m/z: 364 $(M+H)^+$.

(8*S*,9*R*,11*S*)-10-[(*R*)-1-Hydroxyethyl]-5-iminomethyl-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid (4e) To a mixture of **4d** (39 mg, 1.2×10^{-4} mol), CH_3CN (1.3 ml) and phosphate buffer (pH 7.4, 1.3 ml) were added benzyl formimidate hydrochloride (439 mg, 2.55×10^{-3} mol) and *N*,*N*-diisopropylethylamine (270 μl, 1.55×10^{-3} mol) at 0 °C. After being stirred for 1 h, water (5 ml) was added to the reaction mixture. The aqueous solution was washed with diethyl ether, and was concentrated under reduced pressure. The residue was purified by column chromatography on Cosmosil 75C_{18}-PREP (12 ml) using water as eluent and then high pressure liquid chromatography on Cosmosil 5C_{18}-AR (20 mm i.d.×250 mm, Nacalai Tesque) using water as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4e** (5.3 mg, 13%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.29 (3H, d, J=6.4 Hz), 1.50—1.70 (1H, m), 1.95—2.10 (1H, m), 2.95—3.40 (2H, m), 3.09, 3.27 (3H, s×2), 3.45 (1H, dd, J=5.5, 3.2 Hz), 3.56, 3.90, 3.92 (1H, br d×3, J=14 Hz), 4.20—4.35 (2H, m), 4.40—4.95 (3H, m), 5.29, 5.32, 5.86 (1H, br d×3, J=14 Hz), 7.86, 7.89, 8.01 (1H, s×3). IR (KBr): 3370, 1756, 1712, 1652, 1592 cm^{-1}.

(8*S*,9*R*,10*S*)-5-(3-Guanidinopropionyl)-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid (4f) To a mixture of **11f** (70.0 mg, 1.22×10^{-4} mol) and $Pd(PPh_3)_2Cl_2$ (2 mg) in CH_2Cl_2 (4 ml) was added n-Bu_3SnH (200 μl, 7.44×10^{-4} mol) at 0 °C. After being stirred at room temperature for 15 min, hexane (8 ml) was added. Pale yellow precipitates that emerged were collected by filtration and washed with EtOAc. The crude solid thus obtained was purified by column chromatography on Cosmosil 75C_{18}-PREP (10 ml) using water as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4f** (31 mg, 61%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.27 (3H, d, J=6.4 Hz), 1.40—1.65 (1H, m), 1.90—2.05 (1H, m), 2.60—3.15 (3H, m), 3.15—3.35 (1H, m), 3.33, 3.86 (1H, d×2, J=14.0 Hz), 3.42 (1H, dd, J=5.9, 3.2 Hz), 3.40—3.60 (2H, m), 4.10, 4.61 (1H, br d×2, J=13 Hz), 4.20—4.30 (1H, m), 4.29 (1H, dd, J=10.5, 3.2 Hz), 5.49, 5.91 (1H, d×2, J=14.0 Hz). IR (KBr): 3378, 3235, 1763, 1624 cm^{-1}. MS (FAB) m/z: 366 $(M+H)^+$.

Potassium (8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-11-oxo-5-(3-pyridylcarbonyl)-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (4g) To a suspension of **11g** (45.0 mg, 1.13×10^{-4} mol), Pd$(PPh_3)_4$ (1.3 mg) and PPh_3 (1.5 mg) in EtOAc (0.5 ml) was added 0.5 M EtOAc solution of potassium 2-ethylhexanoate (0.24 ml) at room temperature and stirred for 30 min. Pale yellow precipitates that emerged were collected by filtration and washed with EtOAc. The crude solid thus obtained was purified by column chromatography on Cosmosil 75C_{18}-PREP (20 ml) using water as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4g** (29.2 mg, 65%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.27, 1.29 (3H, d×2, J=6.6 Hz), 1.6—1.8 (1H, m), 1.9—2.2 (1H,

m), 3.14, 3.36 (1H, m×2), 3.2—3.4 (1H, m), 3.4—3.5 (1H, m), 3.70, 3.96 (1H, d×2, J=14.0 Hz), 3.85, 4.30 (1H, m×2), 4.20—4.40 (2H, m), 5.23, 6.01 (1H, d×2, J=14.0 Hz), 7.50—7.60 (1H, m), 7.80—8.00 (1H, m), 8.50—8.70 (2H, m). IR (KBr): 3385, 1758, 1606 cm^{-1}.

Potassium (8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-11-oxo-5-(4-pyridylcarbonyl)-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (4h) To a suspension of **11h** (48 mg, 1.2×10^{-4} mol), $Pd(PPh_3)_4$ (1.5 mg) and PPh_3 (1.7 mg) in EtOAc (0.5 ml) was added 0.5 M EtOAc solution of potassium 2-ethylhexanoate (0.27 ml) at room temperature and stirred for 20 min. Pale yellow precipitates that emerged were collected by filtration and washed with EtOAc. The crude solid thus obtained was purified by column chromatography on Cosmosil 75C_{18}-PREP (20 ml) using water as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4h** (29.2 mg, 65%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.27, 1.28 (3H, d×2, J=6.7 Hz), 1.5—1.8 (1H, m), 1.8—2.2 (1H, m), 3.13, 3.33 (1H, m×2), 3.2—3.4 (1H, m), 3.4—3.6 (1H, m), 3.69, 3.97 (1H, d×2, J=14.0Hz), 3.74, 4.61 (1H, m×2), 4.20—4.40 (2H, m), 5.13, 6.00 (1H, d×2, J=14.0 Hz), 7.40—7.60 (2H, m), 8.66 (2H, d, J=5.6 Hz). IR (KBr): 3372, 1759, 1600 cm^{-1}. MS (FAB) m/z: 396 $(M+H)^+$.

(8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylic Acid (4i) To a mixture of **11i** (85.0 mg, 2.26×10^{-4} mol) and $Pd(PPh_3)_2Cl_2$ (7.7 mg) in CH_2Cl_2 (2 ml) was added *n*-Bu_3SnH (0.24 ml, 8.9×10^{-4} mol) at room temperature. After being stirred for 15 min, hexane was added to the reaction mixture. Pale yellow precipitates that emerged were collected by filtration and washed with hexane. The crude solid thus obtained was subjected to column chromatography on Cosmosil 75C_{18}-PREP (10 ml) using water as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4i** (21.4 mg, 38%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.27 (3H, d, J=5.9 Hz), 1.83 (1H, qd, J=13.1, 3.7 Hz), 2.05—2.20 (1H, m), 3.20—3.35 (2H, m), 3.50—3.55 (1H, m), 3.52 (1H, dd, J=5.2, 3.4 Hz), 3.62 (1H, br d, J=13.0 Hz), 3.80 (1H, d, J=13.3 Hz), 4.26 (1H, m), 4.35 (1H, dd, J=10.3, 3.4 Hz), 4.86 (1H, d, J=13.3 Hz). IR (KBr): 3393, 1766, 1601 cm^{-1}. MS (FAB) m/z: 253 $(M+H)^+$.

(8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-5-methyl-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid (4j) To a mixture of **11j** (30.0 mg, 9.79×10^{-5} mol) and $Pd(PPh_3)_2Cl_2$ (4 mg) in CH_2Cl_2 (0.3 ml) was added *n*-Bu_3SnH (80 μl, 2.97×10^{-4} mol) at room temperature. After being stirred for 30 min, water (5 ml) was added to the reaction mixture. The mixture was washed with EtOAc and the aqueous layer was concentrated to *ca.* 1 ml under reduced pressure. The aqueous solution thus obtained was subjected to column chromatography on Cosmosil 75C_{18}-PREP (5 ml) using water as eluent. Combined eluates were concentrated to *ca.* 5 ml under reduced pressure and then lyophilized to give **4j** (16.6 mg, 64%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.30 (3H, d, J=6.4 Hz), 1.85—2.05 (1H, m), 2.10—2.25 (1H, m), 2.96 (3H, s), 3.20—3.40 (2H, m), 3.56 (1H, dd, J=5.6, 3.5 Hz), 3.68 (1H, br d, J=12 Hz), 3.82 (1H, br d, J=13 Hz), 4.20—4.35 (1H, m), 4.39 (1H, dd, J=10.5, 3.5 Hz), 4.94 (1H, br d, J=13 Hz). IR (KBr): 3381, 1764, 1603 cm^{-1}. MS (FAB) m/z: 267 $(M+H)^+$.

(8*S*,9*R*,11*S*)-10-[(*R*)-1-Hydroxyethyl]-5-(carbamoyl)methyl-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid (4k) To a mixture of **11k** (30 mg, 8.6×10^{-5} mol) and $Pd(PPh_3)_2Cl_2$ (0.7 mg) in CH_2Cl_2 (1.5 ml) was added *n*-Bu_3SnH (50 μl, 1.7×10^{-4} mol) at room temperature. After being stirred for 10 min, water (10 ml) and methanol (0.5 ml) were added to the reaction mixture. The mixture was washed with EtOAc and the aqueous phase was concentrated to *ca.* 1 ml under reduced pressure, and was subjected to column chromatography on Cosmosil 75C_{18}-PREP (5 ml) using water as eluent. Combined eluates were concentrated to *ca.* 5 ml under reduced pressure and then lyophilized to give **4k** (17.5 mg, 66%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.27 (3H, d, J=6.4 Hz), 1.90—2.25 (2H, m), 3.20—3.50 (2H, m), 3.55 (1H, dd, J=5.6, 3.5 Hz), 3.65—3.75 (1H, m), 3.92 (1H, br d, J=13 Hz), 4.05 (2H, s), 4.28 (1H, m), 4.37 (1H, dd, J=10.4, 3.5 Hz), 4.94 (1H, br d, J=13 Hz). IR (KBr): 3388, 1765, 1694, 1603 cm^{-1}. MS (FAB) m/z: 310 $(M+H)^+$.

Potassium (8*S*,9*R*,10*S*)-5-Carbamoyl-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (4l) To a solution of **11l** (28.5 mg, 8.50×10^{-5} mol), $Pd(PPh_3)_4$ (1.5 mg) and PPh_3 (1.7 mg) in a mixture of THF, CH_2Cl_2 and methanol (10 : 10 : 1, 2 ml) was added 0.5 M EtOAc solution of potassium 2-ethylhexanoate (170 μl) at room temperature and stirred for 15 min. Pale yellow precipitates that emerged were collected by filtration and washed with EtOAc. The crude solid thus obtained was purified by column chromatography on Cosmosil 75C_{18}-PREP (10 ml) using water as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4l** (29.2 mg, 65%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.28 (3H, d, J=6.5 Hz), 1.55 (1H, qd, J=12.5, 4.0 Hz), 1.85—2.00 (1H, m), 3.05 (1H, ddd, J=14, 12, 2 Hz), 3.24 (1H, br td, J=11, 5 Hz), 3.44 (1H, dd, J=5.8, 3.3 Hz), 3.73 (1H, d, J=15.0 Hz), 4.18 (1H, br d, J=14 Hz), 4.20—4.30 (1H, m), 4.29 (1H, dd, J=10.4, 3.3 Hz), 5.13 (1H, d, J=15.0 Hz). IR (KBr): 3357, 1775, 1657, 1595 cm^{-1}. MS (FAB) m/z: 334 $(M+H)^+$.

(8*S*,9*R*,10*S*)-5-[(Guanidino)carbonyl]-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid (4m) To a mixture of **11m** (47.0 mg, 1.02×10^{-4} mol) and $Pd(PPh_3)_2Cl_2$ (4 mg) in CH_2Cl_2 (0.5 ml) was added *n*-Bu_3SnH (260 μl, 9.66×10^{-4} mol) at room temperature. After being stirred for 45 min, water (5 ml) was added to the reaction mixture. The mixture was washed with EtOAc and the aqueous phase was concentrated to *ca.* 1 ml under reduced pressure. The aqueous solution thus obtained was subjected to column chromatography on Cosmosil 75C_{18}-PREP (5 ml) using a mixture of water and CH_3CN (98 : 2) as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4m** (6.1 mg, 18%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.29 (3H, d, J=6.4 Hz), 1.64 (1H, qd, J=12.5, 4.1 Hz), 1.95—2.05 (1H, m), 3.19 (1H, br t, J=13 Hz), 3.35—3.40 (1H, m), 3.46 (1H, dd, J=5.8, 3.3 Hz), 3.83 (1H, br d, J=15 Hz), 4.20—4.40 (2H, m), 4.34 (1H, dd, J=10.3, 3.3 Hz), 5.10—5.50 (1H, m). IR (KBr): 3354, 1762, 1698, 1593 cm^{-1}.

(8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-11-oxo-5-[(pyroridin-3-yl)carbamoyl]-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid (4n) To a mixture of **11n** (38.0 mg, 1.02×10^{-4} mol) and $Pd(PPh_3)_2Cl_2$ (1 mg) in CH_2Cl_2 (1 ml) was added *n*-Bu_3SnH (84 μl, 3.1×10^{-4} mol) at room temperature. After being stirred for 30 min, water (5 ml) was added to the reaction mixture. The mixture was washed with EtOAc and the aqueous phase was concentrated to *ca.* 1 ml under reduced pressure. The aqueous solution thus obtained was subjected to column chromatography on Cosmosil 75C_{18}-PREP (5 ml) using a mixture of water and CH_3CN (1 : 0 to 99 : 1) as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4n** (12.6 mg, 44%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.27 (3H, d, J=6.4 Hz), 1.40—1.55 (1H, m), 1.85—2.15 (2H, m), 2.20—2.40 (1H, m), 3.00—3.15 (1H, m), 3.20—3.45 (4H, m), 3.50—3.60 (2H, m), 3.74, 3.74 (1H, d×2, J=15.1 Hz), 4.15—4.50 (4H, m), 4.92, 4.99 (1H, br d×2, J=15 Hz). IR (KBr): 3367, 2967, 1760, 1626, 1600, 1541 cm^{-1}. MS (FAB) m/z: 365 $(M+H)^+$.

Potassium (8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-5-(*N*-methyl)thiocarbamoyl-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylate (4o) To a mixture of **11o** (48.0 mg, 1.31×10^{4} mol), $Pd(PPh_3)_4$ (1 mg) and PPh_3 (5 mg) in EtOAc (1 ml) was added 0.5 M EtOAc solution of potassium 2-ethylhexanoate (500 μl) at room temperature. After being stirred for 90 min, EtOAc (2 ml) was added and the mixture was extracted with water (3 ml×3 times). Combined aqueous layers were concentrated under reduced pressure and subjected to column chromatography on Cosmosil 75C_{18}-PREP (10 ml) using water as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4o** (28.6 mg, 60%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.26 (3H, d, J=6.2 Hz), 1.58 (1H, qd, J=12.5, 4.0 Hz), 1.90—2.00 (1H, m), 3.03 (3H, s), 3.25—3.40 (2H, m), 3.42 (1H, dd, J=5.8, 3.2 Hz), 3.88 (1H, d, J=14.8 Hz), 4.23 (1H, m), 4.30 (1H, dd, J=10.3, 3.2 Hz), 5.05 (1H, br d, J=14.0 Hz), 5.23 (1H, dd, J=14.8, 1.8 Hz). IR (KBr): 3250, 1754, 1699 cm^{-1}. MS (FAB) m/z: 364 $(M+H)^+$.

(8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-11-oxo-5-[(pyroridin-3-yl)thiocarbamoyl]-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid (4p) To a mixture of **11p** (100 mg, 1.98×10^{-4} mol) and $Pd(PPh_3)_2Cl_2$ (2.8 mg) in CH_2Cl_2 (2 ml) was added *n*-Bu_3SnH (213 μl, 7.92×10^{-4} mol) at room temperature. After being stirred for 30 min, water (5 ml) was added to the reaction mixture. The mixture was washed with hexane and the aqueous phase was concentrated to *ca.* 1 ml under reduced pressure. The aqueous solution thus obtained was subjected to column chromatography on Cosmosil 75C_{18}-PREP (10 ml) using a mixture of water and CH_3CN (1 : 0 to 9 : 1) as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4p** (24 mg, 32%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.26 (3H, d, J=6.4 Hz), 1.50—1.70 (1H, m), 1.90—2.00 (1H, m), 2.00—2.25 (1H, m), 2.30—2.50 (1H, m), 3.05—3.75 (7H, m), 3.92, 3.93 (1H, d×2, J=14.8 Hz), 4.15—4.35 (2H, m), 4.95—5.20 (2H, m), 5.24, 5.27 (1H, br d×2, J=15 Hz). IR (KBr): 3413, 3239, 1761, 1589 cm^{-1}. MS (FAB) m/z: 381 $(M+H)^+$.

(8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-5-iminomethyl-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid (4q) To a mixture of **4i** (62.0 mg, 2.46×10^{-4} mol), CH_3CN (0.9 ml) and phosphate buffer (pH 7.4, 0.9 ml) were added benzyl formimidate hydrochloride (204 mg,

1.19×10^{-3} mol) and *N*,*N*-diisopropylethylamine (210 μl, 1.21×10^{-3} mol) at 0 °C. After being stirred for 30 min, water (5 ml) was added to the reaction mixture. The aqueous solution was washed with diethyl ether, and was concentrated under reduced pressure. The residue was purified by column chromatography on Cosmosil 75C_{18}-PREP (10 ml) using water as eluent followed by HPLC on Cosmosil 5C_{18}-AR (20 mm i.d.×250 mm, Nacalai Tesque) using water as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4q** (17.6 mg, 27%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.30 (3H, d, J=6.5 Hz), 1.65—1.90 (1H, m), 2.05—2.20 (1H, m), 3.25—3.45 (2H, m), 3.50 (1H, dd, J=5.6, 3.5 Hz), 3.70, 3.95 (1H, d×2, J=14.0 Hz), 4.00, 4.15 (1H, m×2), 4.20—4.35 (1H, m), 4.37 (1H, dd, J=10.5, 3.4 Hz), 5.26, 5.43 (1H, d×2, J=14.4 Hz), 7.85, 7.90 (1H, s×2). IR (KBr): 3367, 1777, 1578 cm^{-1}. MS (FAB) *m*/*z*: 280 $(M+H)^+$.

(8*S*,9*R*,10*S*)-10-[(*R*)-1-Hydroxyethyl]-5-acetimidoyl-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid (4r) To a mixture of **11f** (27 mg, 6.5×10^{-5} mol) and $Pd(PPh_3)_2Cl_2$ (2.4 mg) in CH_2Cl_2 (0.3 ml) was added *n*-Bu_3SnH (90 μl, 3.3×10^{-4} mol) at room temperature. After being stirred for 30 min, water (5 ml) was added. The mixture was washed with EtOAc and the aqueous phase was concentrated to *ca.* 1 ml under reduced pressure. The aqueous solution thus obtained was subjected to column chromatography on Cosmosil 75C_{18}-PREP (5 ml) using water as eluent. Combined eluates were concentrated to *ca.* 10 ml under reduced pressure and then lyophilized to give **4r** (8.4 mg, 45%) as a colorless powder. ^{1}H-NMR (D_2O) δ: 1.30 (3H, d, J=6.4 Hz), 1.65—1.85 (1H, m), 2.05—2.20 (1H, m), 2.35, 2.42 (3H, s×2), 3.30—3.60 (2H, m), 3.47 (1H, dd, J=5.6, 3.5 Hz), 3.96, 4.03 (1H, d×2, J=14.3 Hz), 4.10—4.35 (2H, m), 4.37 (1H, dd, J=10.3, 3.5 Hz), 5.34, 5.56 (1H, d×2, J=14.3, 1.5 Hz). IR (KBr): 3335, 1760, 1673, 1609 cm^{-1}. MS (FAB) *m*/*z*: 294 $(M+H)^+$.

(8*S*,9*R*,10*S*)-5-Amidino-10-[(*R*)-1-hydroxyethyl]-11-oxo-1,5-diazatricyclo[7.2.0.0^{3,8}]undec-2-ene-2-carboxylic Acid 2/3 Hydrate (4s) To a mixture of **11s** (176 mg, 3.50×10^{-4} mol) and $Pd(PPh_3)_2Cl_2$ (5 mg) in CH_2Cl_2 (7 ml) was added *n*-Bu_3SnH (565 μl, 2.10×10^{-3} mol) at room temperature. After being stirred for 15 min, hexane was added to the reaction mixture. Pale yellow precipitates that emerged were collected by filtration and washed with hexane. The crude solid thus obtained was subjected to column chromatography on Cosmosil 75C_{18}-PREP (20 ml) using water as eluent. Crystalline precipitates were emerged during concentration of the combined eluates under reduced pressure. The precipitates were collected by filtration and washed with cold water to give **4s** (31 mg, 29%) as colorless crystals, mp 208 °C (dec.). ^{1}H-NMR (D_2O) δ: 1.27 (3H, d, J=6.3 Hz), 1.64 (1H, qd, J=12.6, 4.0 Hz), 1.95—2.05 (1H, m), 3.25—3.35 (1H, m), 3.35—3.45 (1H, m), 3.44 (1H, dd, J=6.3, 3.4 Hz), 3.85 (1H, d, J=14.6 Hz), 4.00—4.10 (1H, m), 4.25 (1H, quintet, J=6.3 Hz), 4.32 (1H, dd, J=10.2, 3.4 Hz), 5.07 (1H, dd, J=14.6, 1.9 Hz). IR (KBr): 3483, 3371, 3204, 1732, 1684, 1654, 1604 cm^{-1}. *Anal.* Calcd for $C_{13}H_{18}N_4O_4$ 3/2H_2O: C, 48.59; H, 6.59; N, 17.44. Found: C, 48.36; H, 6.78; N, 17.39. MS (FAB) *m*/*z*: 295 $(M+H)^+$.

Measurement of Antibacterial Activity MICs were measured on Nutrient agar (Eiken Chemical Ltd.) by the twofold dilution method. The inoculum size of the bacteria was one-loopful of 107 cfu/ml.

Determination of Urinary Recovery Urine was collected at 8 and 24 h after administration. Excretion as the parent 5-formimidoyl-5-azatrinem **4q** was determined by bioassay using *Bacillus subtilis* ACTT6633. Urinary recovery (%, 0—24 h) was calculated based on the excretion and the initial dose.

References and Notes

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9) Decarboxylation of the NH unprotected compound **7a** under these reaction conditions afforded a 3 : 7 diastereomeric mixture of the decarboxylated products with predominant formation of the undesired diastereoisomer. For a similar stereochemical aspect of the decarboxylation reaction, see reference 8.
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