Synthesis of 1,2-Disubstituted-1-carbacephem

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Various kinds of 1,2-disubstituted-1-carbacephems were synthesized by employing several electrophilic reactions (*e.g.* oxidation, halogenation, halogenohydrination) toward the aldehyde 2 followed by cyclization, and also from 1,2-dehydro-1-carbacephem 10. The stereochemistry of the 1,2-disubstituted-1-carbacephems prepared was determined by proton nuclear magnetic resonance (^{1}H-NMR) analysis. The diol 4a, chlorohydrin 15a and bromohydrin 17a were converted to the corresponding 7-N-acylated compounds 27a—c. Antibacterial activities of 27a—c, however, were rather low compared with those of KT 3919 (non-substituted carbacephem) and KT 3933 (2α-hydroxy carbacephem), which are the racemates of KT 3767 and KT 3937, respectively.

Keywords β-lactam; carbacephem; 1,2-disubstituted-carbacephem; halogenation; halogenohydrination; oxidation; stereochemistry; ^{1}H-NMR; acylation; antibacterial activity

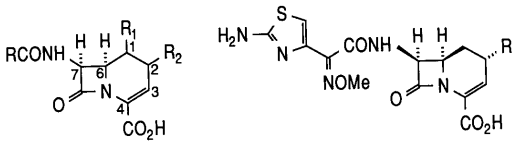
We have already reported the synthesis of 3-*H*-1-carbacephem KT 3767[1] which showed a broad antibacterial spectrum toward gram-negative bacteria. In addition, 2-hydroxy-3-*H*-1-carbacephem KT 3937[2] showed an antibacterial activity spectrum that extended to *Pseudomonas aeruginosa*. This fact prompted us to investigate further nuclear analogs of carbacephem.

Here we wish to report the synthesis of 1,2-disubstituted-1-carbacephems **1**; this substitution pattern is characteristic of the carbacephem nucleus, being unavailable in the cephem or 1-oxacephem nucleus. The compounds prepared had a variety of configurations at C-1 and C-2, as determined by proton nuclear magnetic resonance (^{1}H-NMR) analysis.

First several electrophilic reactions toward the α,β-unsaturated aldehyde **2**, which was the key intermediate for 1,2-dehydro-1-carbacephem **10**,[3] were examined. Oxidation of **2** with H_2O_2–OsO_4[4] afforded the diols **3a** and **3b** which, without isolation, were cyclized by dimethylethanolamine to the bicyclic products **4a** and **4b** as a mixture of stereoisomers in the ratio of 3 : 1. Isomers **4a** and **4b** were the consequence of OsO_4 oxidation from both sides of the double bond.

Bromine addition to **2** proceeded readily at 0 °C, and spontaneous elimination afforded the α-bromo-α,β-unsaturated aldehyde **5** in moderate yield. This aldehyde was cyclized easily with dimethylethanolamine to give 2-bromo-1,2-dehydro-1-carbacephem **6** in good yield.

Epoxidation of **2** was carried out with H_2O_2–NaOH in MeOH to afford the epoxyaldehyde **7** in considerable yield.



1

KT 3767: R = H
KT 3937: R = OH

Fig. 1

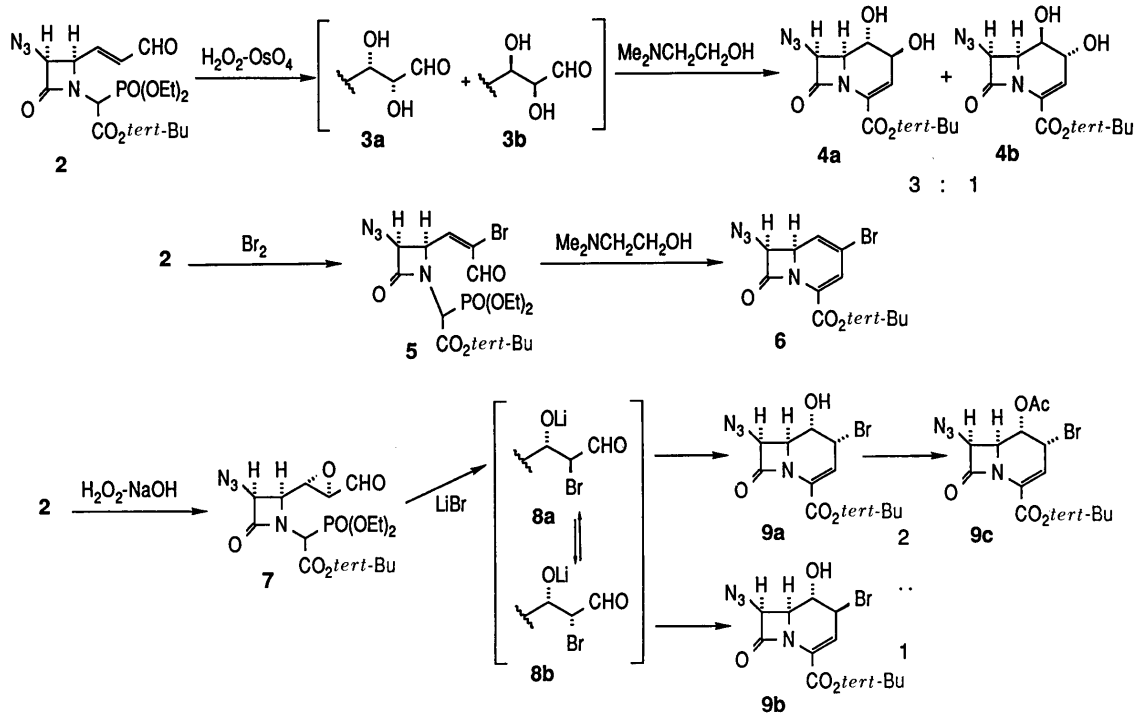


Chart 1

Subsequent treatment of **7** with LiBr gave the cyclic bromohydrins **9a** and **9b** in the ratio of 2:1. Epoxide opening by bromide anion resulted in the formation of lithium alkoxide, which acted as a base for intramolecular Horner–Emmons reaction. The regiochemistry of **9a** was determined by comparison of the chemical shifts of 1-H and 2-H in **9a** and those of its acetylated compound **9c**. That is, the signal of 1-H was shifted downfield 0.81 ppm in **9c**, in contrast with that of 2-H which was shifted only 0.17 ppm. The stereoisomer **9b** was presumably obtained *via* epimerization of **8a** to **8b** (Chart 1). The identical configuration at C-1 in **9a** and **9b** indicated that epoxidation had occurred stereoselectively to afford solely **7**.

Secondly we carried out several electrophilic reactions with 1,2-dehydro-1-carbacephem **10**. Chlorination was effected with molecular chlorine affording the 1β,2α-dichloride **12** exclusively, suggesting diaxial opening of the β-chloronium ion **11**. Upon treatment of the dichloride **12** with Ag_2CO_3/H_2O–acetone, the allylic chloride was hydrolyzed to give the 2α-hydroxide **15a** (path a), while double bond rearrangement took place with $AgBF_4/H_2O$–acetone, generating the isomer **15b** predominantly (path b). The configuration at C-4 in **15b** was not determined. Isomerization of **15b** to the desired **15a** was accomplished easily with CF_3CO_2H. The retention of C-2 configuration in **15a** was the consequence of attack of hydroxide anion on the intermediate **14** from the less-hindered α-side. Direct chlorohydrination and chloroformyloxylation of **10** were attempted with $ClSiMe_3$–H_2O_2[5] and *N*-chlorosuccinimide/dimethylformamide (DMF)[6] respectively, but the dichloride **12** was the only product isolated in both cases. 1,8-Diazabicyclo[5.4.0]undec-7-ene(DBU) was employed for the elimination of 1 mol of hydrogen chloride in **12** to give the 2-chloro-1,2-dehydro carbacephem **13**.

In contrast to chlorohydrination, bromohydrination of **10** with *N*-bromosuccinimide–H_2O proceeded readily.[7] The 1,4-bromohydrin **17b** was formed mainly when the reaction was run in dimethoxyethane, while the 1,2-bromohydrin **17a** was predominant in dimethylsulfoxide. The regiochemistry of **17a** was determined by comparison of the ^{1}H-NMR spectra of **17a** and the corresponding acetate **17c**.

In the same manner, iodohydrination of **10** was carried out with I_2–KIO_3[8] affording **18a** and **18b**, in the ratio of *ca.* 3:2. Different from the chlorohydrin **15b**, the iodohydrin **18b** could not be converted to **18a** under various conditions examined.

In bromine addition to **10**, the 1β,2α-dibromide **21** could not be isolated, as was the case with dichlorination. The 1α,2α-dibromide **20** was obtained in a small amount as a sole isolated product. It could be postulated that the carbocation **19** was produced first, and subsequently attacked at the C-2 position by bromide anion from the α-side.

Since the 1,2-epoxide was of interest, we attempted epoxidation of **10** with *m*-chloroperbenzoic acid. As was anticipated, the epoxide was so unstable that reaction with *m*-chlorobenzoic acid occurred to give the 1-hydroxy-2-benzoates **23a** and **23b**, instead of the epoxide. Addition of K_2CO_3 to trap *m*-chlorobenzoic acid resulted in recovery of the starting material **10**. The coincidence of C-2 configuration in **23a** and **23b** suggested the formation of the carbocations **22a** and **22b** as intermediates.

1,2-Disubstituted-1-carbacephems so far prepared have

Chart 2

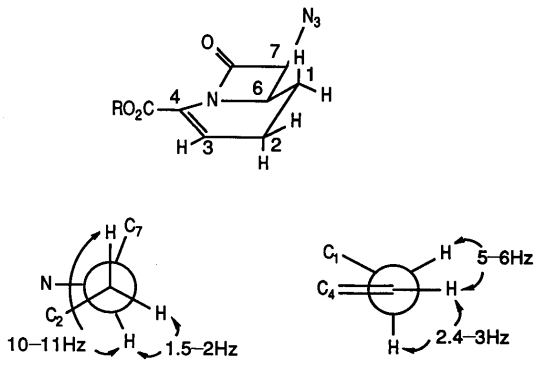
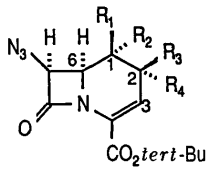


Fig. 2

TABLE I. ^{1}H-NMR Data



No.	R				ppm			J (Hz)		
	1	2	3	4	1-H	2-H	3-H	6H—1H	2H—3H	1H—2H
9a	H	OH	H	Br	4.05	5.0	6.4		6	3.5
9c	H	OAc	H	Br	4.91	5.17	6.38	10.5	6.0	4.2
20	H	Br	H	Br	4.17	4.92	6.39	11.3	6.0	3.6
23a	H	OH	H	OCOAr	4.23	5.81	6.31	10.7	5.6	3.8
4a	H	OH	OH	H	3.66	4.26	6.11	10.6	2.4	7.5
9b	H	OH	Br	H	4.2	4.6	6.3	10	3	9
4b	OH	H	H	OH	4.07	4.07	6.27	1.5	6.4	
12	Cl	H	H	Cl	4.57	4.71	6.25	2.0	5.5	2.2
15a	Cl	H	H	OH	4.34	4.45	6.28	2.0	5.4	2.4
17a	Br	H	H	OH	4.4	4.6	6.3	2	6	3
17c	Br	H	H	OAc	4.38	5.55	6.22	2.3	5.4	2.4
18a	I	H	H	OH	4.35	4.71	6.24		5	
23b	OH	H	H	OCOAr	4.36	5.52	6.35	1.6	5.1	2.3

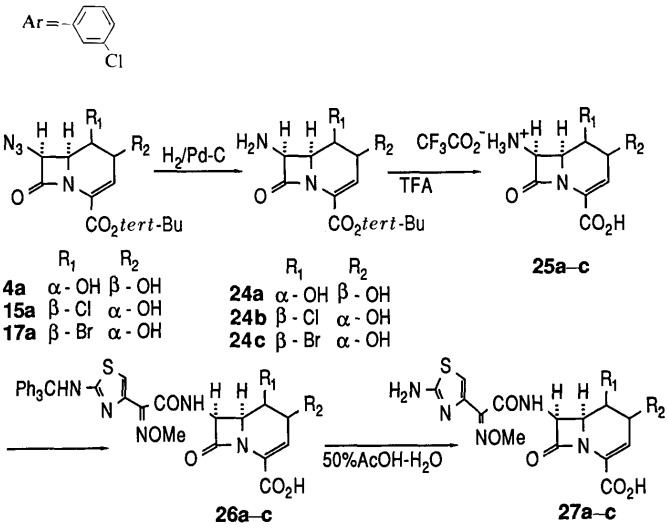
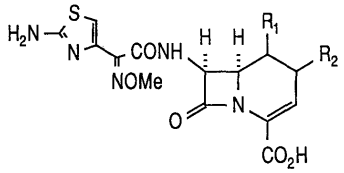


Chart 3

TABLE II. Minimal Inhibitory Concentration Values (μg/ml)



	R1	R2
27a	α-OH	β-OH
b	β-Cl	α-OH
c	β-Br	α-OH
KT3919	H	α-OH
KT3933	H	β-OH

	27a	27b	27c	KT3919	KT3933
S. aureus 209-p	>100	>50	>100	12.5	50
E. coli GN2411-5	>100	3.12	6.25	0.05	0.2
K. pneumoniae 8045	>100	1.56	1.56	0.02	0.05
S. marcescens T-26	>100	25	50	0.04	3.12
P. mirabilis 1287	>100	6.25	3.12	0.1	0.2

Müeller Hinton agar dilution method. Inoculum size 10^6 cfu.

had three type of configurations at C-1 and C-2, namely, 1α2α, 1α2β and 1β2α, as determined by ^{1}H-NMR analysis. Pseudo chair form of the six-membered ring in 1-carbacephem was postulated as the most stable conformation (Fig. 2). The assignment of the configurations at C-1 and C-2 was based on the coupling constants between 6-H and 1-H, 2-H and 3-H, respectively. That is, 6-H and 1β-H have a large (10-11 Hz) coupling constant, while 6-H and 1α-H have a small one (1.5—2 Hz). In the same manner, 2β-H and 3-H have a larger (5—6 Hz) coupling constant than 2α-H and 3-H (Fig. 2). In addition, the coupling constant between 1-H and 2-H substantiates the above assignment. The NMR data are summarized in Table I. The coupling constant between 2-H and 3-H (5 Hz) of the iodohydrin **18a** indicates 2β-H. Despite the ambiguity between 6-H and 1-H (also 1-H and 2-H), 1α-H is estimated from the *trans* addition of the iodohydrin, analogous to that of the bromohydrin **17a**.

Among these 1,2-disubstituted-1-carbacephems, the diol **4a**, chlorohydrin **15a** and bromohydrin **17a** were selected for the preparation of acylated compounds. The procedure is shown in Chart 3. Catalytic hydrogenation of the azide, ester hydrolysis with CF_3CO_2H and acylation with 2-(2-tritylamino-4-thiazolyl)-2-(*Z*)-methoxyiminoacetyl chloride followed by deprotection afforded the desired compounds **27a—c**. Unfortunately the antibacterial activities of **27a—c** appeared to be low compared with those of KT 3919 and KT 3933, which are the racemates of KT 3767 and KT 3937, respectively (Table II). These data may not be sufficient to evaluate the biological activity of 1,2-disubstituted-1-carbacephems, however, it seems that the target enzyme of tested organisms has a rather narrow tolerance for structural modification at C-1, although a cephem 1β-oxide has been reported to retain good antimicrobial activity.[9]

Experimental

Infrared (IR) spectra were measured with a JASCO IR-810, and ^{1}H-NMR

spectra on Varian T-60 and JEOL GNM PS-100 spectrometers. Mass spectra were measured with a JEOL JMS-01SG-2. For column chromatography, silica gel (SiO_2, Wako C-200) or highly porous polymer resin (Mitsubishi Kasei Diaion HP-10 or HP-20AG) was used unless otherwise specified. Thin-layer chromatography (TLC) was performed on Silica gel 60 F_{254} plates (Merck). All organic solvent extracts were dried over anhydrous sodium sulfate.

***tert*-Butyl (4*S**,5*S**,6*S**,7*S**)-7-Azido-4,5-dihydroxy-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 4a and *tert*-Butyl (4*R**,5*R**,6*S**,7*S**)-7-Azido-4,5-dihydroxy-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 4b** OsO_4 (80 mg) and 30% H_2O_2 (4.6 ml) were added to a solution of the aldehyde **2** (3.68 g) in ether (140 ml), and the mixture was stirred at room temperature for 1 h. Then further OsO_4 (200 mg) in tetrahydrofuran (THF) (4 ml) and 30% H_2O_2 (1.5 ml) were added. The mixture was stirred for 7 h, diluted with AcOEt, washed with brine, dried and evaporated. The residue was dissolved in benzene (50 ml), dimethylethanolamine (0.91 ml) was added, and the mixture was stirred at 40 °C for 3 h. It was diluted with AcOEt, washed with saturated NH_4Cl and brine, dried and evaporated. The residue was purified by column chromatography (SiO_2 150 g, *n*-hexane : AcOEt = 2 : 1) to afford **4a** (128 mg: 4.9%) and **4b** (45 mg: 1.7%). **4a**; ^{1}H-NMR (CD_3OD) ppm: 6.11 (1H, d, J = 2.4 Hz), 5.16 (1H, d, J = 4.5 Hz), 4.26 (1H, dd, J = 7.5, 2.4 Hz), 3.83 (1H, dd, J = 10.6, 4.5 Hz), 3.66 (1H, dd, J = 10.6, 7.5 Hz), 1.50 (S, 9H). IR (KBr): 2120, 1790, 1780, 1720, 1635 cm^{-1}. **4b**; ^{1}H-NMR (CD_3OD) ppm: 6.27 (1H, d, J = 6.4 Hz), 5.06 (1H, d, J = 5.4 Hz), 4.07 (2H, m), 3.79 (1H, dd, J = 5.4, 1.5 Hz), 1.52 (9H, s). IR (KBr): 2130, 1795, 1780, 1720—40, 1700, 1630, 1620 cm^{-1}.

***tert*-Butyl (±)-2-[3,4-*cis*-3-Azido-4-(2-bromo-3-oxo-1-propenyl)-2-oxoazetidin-1-yl]-2-diethylphosphonoacetate 5** A 1 M solution of bromine in CCl_4 (2.85 ml) was added slowly to a solution of the aldehyde **2** (520 mg) in CCl_4 (5 ml) under ice-cooling. The mixture was stirred at 0 °C for 2 h 15 min. The solvent was evaporated off *in vacuo* and the residue was purified by column chromatography (SiO_2 25 g, *n*-hexane : AcOEt = 1 : 2) to give **5** (363 mg: 58.7%). IR ($CHCl_3$): 2130, 1790, 1750, 1720 cm^{-1}.

***tert*-Butyl (6*R**,7*S**)-7-Azido-4-bromo-8-oxo-1-azabicyclo[4.2.0]oct-2,4-diene-2-carboxylate 6** Dimethylethanolamine (0.055 ml) was added to a solution of the bromoaldehyde **5** (274 mg) in benzene (3 ml), and the mixture was stirred at room temperature for 1 h 10 min. After dilution with AcOEt, the mixture was washed with saturated NH_4Cl, brine and dried. The solvent was evaporated off to afford **6** (175 mg: 92.7%). ^{1}H-NMR ($CDCl_3$) ppm: 6.60 (1H, s), 6.23 (1H, m), 5.30 (1H, d, J = 5 Hz), 4.65 (1H, dd, J = 5, 2 Hz), 1.53 (9H, s). IR (KBr): 2130, 1795, 1720, 1615 cm^{-1}. Electron impact mass spectra (EIMS) (*m/z*): 341 (m^+).

***tert*-Butyl (±)-2-[3,4-*cis*-3-Azido-4-(1,2-epoxy-3-oxo-propyl)-2-oxoazetidin-1-yl]-2-diethylphosphonoacetate 7** The aldehyde **2** (312 mg) was dissolved in MeOH (30 ml) and treated at −40 °C with 30% H_2O_2 (1.5 ml) and 2 N NaOH (0.45 ml). The mixture was stirred at −40—0 °C for 1 h 50 min. After addition of saturated NH_4Cl, the resulting solution was extracted with $CHCl_3$. The organic layer was separated, washed with brine and dried. Concentration gave **7** (270 mg: 83.3%). IR ($CHCl_3$): 2130, 1785, 1745 cm^{-1}. EIMS (*m/z*): 433 $(M+1)^+$.

***tert*-Butyl (4*R**,5*S**,6*S**,7*S**)-7-Azido-4-bromo-5-hydroxy-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 9a and *tert*-Butyl (4*S**,5*S**,6*S**,7*S**)-7-Azido-4-bromo-5-hydroxy-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 9b** The epoxyaldehyde **7** (234 mg) in benzene (6 ml) and hexamethylphosphoric triamide (HMPA) (0.85 ml) was treated with LiBr (55 mg). The mixture was stirred at room temperature for 28 h, then diluted with ether, washed with brine, dried and evaporated. The residue was purified by column chromatography (SiO_2 10 g, *n*-hexane : AcOEt = 4 : 1) to give **9a** (48.0 mg: 24.7%) and **9b** (26.5 mg: 13.6%). **9a**; ^{1}H-NMR ($CDCl_3$) ppm: 6.4 (1H, d, J = 6 Hz), 5.2 (1H, d, J = 5 Hz), 5.0 (1H, dd, J = 6, 3.5 Hz), 4.05 (2H, m), 1.52 (9H, s). IR ($CHCl_3$): 2120, 1795, 1730, 1625 cm^{-1}. **9b**; ^{1}H-NMR ($CDCl_3$) ppm: 6.3 (1H, d, J = 3 Hz), 5.1 (1H, d, J = 5 Hz), 4.6 (1H, dd, J = 9, 3 Hz), 4.2 (1H, dd, J = 10, 9 Hz), 3.8 (1H, dd, J = 10, 5 Hz), 1.52 (9H, s). IR ($CHCl_3$): 2120, 1790, 1725, 1625 cm^{-1}.

***tert*-Butyl (4*R**,5*S**,6*S**,7*S**)-5-Acetoxy-7-azido-4-bromo-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 9c** Ac_2O (0.5 ml) was added to a solution of **9a** (60 mg) in pyridine (2 ml). The mixture was allowed to stand at room temperature for 5 h, then poured into ice-water and extracted with AcOEt. The organic layer was washed with brine, dried and then evaporated. The residue was purified by column chromatography (SiO_2 3 g, *n*-hexane : AcOEt = 7 : 1) to afford **9c** (25 mg: 37.3%). ^{1}H-NMR ($CDCl_3$) ppm: 6.38 (1H, d, J = 6.0 Hz), 5.17 (1H, dd, J = 6.0, 4.2 Hz), 5.12 (1H, d, J = 5.0 Hz), 4.91 (1H, dd, J = 10.5, 4.2 Hz), 4.28 (1H, dd, J = 10.5, 5.0 Hz), 2.18 (3H, s), 1.53 (9H, s). IR (KBr): 2125, 1800, 1780, 1730 cm^{-1}.

***tert*-Butyl (4*R**,5*R**,6*S**,7*S**)-7-Azido-4,5-dichloro-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 12** A 3 M solution of Cl_2 in CCl_4 (1 ml) was added slowly to a solution of the 1,2-dehydro-1-carbacephem **10** (625 mg) in CH_2Cl_2 (8 ml) at −78 °C. The mixture was allowed to warm to −20 °C in 1 h. Then it was washed with cold aqueous $NaHSO_3$, aqueous $NaHCO_3$ and brine, and evaporated. The residue was purified by column chromatography (SiO_2 30 g, *n*-hexane : AcOEt = 4 : 1) to afford **12** (515 mg: 65%). ^{1}H-NMR ($CDCl_3$) ppm: 6.25 (1H, d, J = 5.5 Hz), 5.13 (1H, d, J = 5.6 Hz), 4.71 (1H, dd, J = 5.5, 2.2 Hz), 4.57 (1H, m), 4.34 (1H, dd, J = 5.6, 2.0 Hz), 1.55 (9H, s). IR ($CHCl_3$): 2130, 1800, 1730, 1630 cm^{-1}. *Anal.* Calcd for $C_{12}H_{14}Cl_2N_4O_3$: C, 43.26; H, 4.23; N, 16.82. Found: C, 43.04; H, 4.16; N, 16.78.

***tert*-Butyl (6*R**,7*S**)-7-Azido-4-chloro-8-oxo-1-azabicyclo[4.2.0]oct-2,4-diene-2-carboxylate 13** The 1,2-dichloride **12** (609 mg) in benzene (6 ml) was treated with DBU (0.445 ml) at 60 °C for 20 min. The mixture was diluted with AcOEt, washed with saturated NH_4Cl and brine, dried and evaporated. The residue was chromatographed (SiO_2 35 g, *n*-hexane : AcOEt = 4 : 1) to give **13** (248 mg: 45.8%). ^{1}H-NMR ($CDCl_3$) ppm: 6.50 (1H, d, J = 1.2 Hz), 5.97 (1H, dd, J = 1.7, 1.2 Hz), 5.26 (1H, d, J = 4.5 Hz), 4.69 (1H, dd, J = 4.5, 1.7 Hz), 1.52 (9H, s). IR ($CHCl_3$): 2130, 2110, 1795, 1725, 1620 cm^{-1}. EIMS (*m/z*): 296 (M^+).

***tert*-Butyl (4*R**,5*R**,6*S**,7*S**)-7-Azido-5-chloro-4-hydroxy-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 15a** Method A (from **12**): Ag_2CO_3 (165 mg) was added to a solution of **12** (200 mg) in 2% H_2O–acetone (6.8 ml). The mixture was stirred at 60 °C for 3.5 h and at 80 °C for 2 h 10 min. It was diluted with AcOEt, washed with brine, dried and evaporated. The residue was purified by column chromatography (SiO_2 12 g, *n*-hexane : AcOEt = 5 : 2) to give **15a** (21.6 mg: 11.4%). ^{1}H-NMR ($CDCl_3$) ppm: 6.28 (1H, d, J = 5.4 Hz), 5.10 (1H, d, J = 5.6 Hz), 4.45 (1H, dd, J = 5.4, 2.4 Hz), 4.34 (1H, m), 4.12 (1H, dd, J = 5.6, 2.0 Hz), 1.54 (9H, s). IR ($CHCl_3$): 3426, 1801, 1797, 1736 cm^{-1}.

Method B (from **15b**): The 1-chloro-4-hydroxy compound **15b** (100 mg) was treated with 20% trifluoroacetic acid (TFA)–CH_2Cl_2 (2 ml) for 2 h under ice-cooling. The mixture was concentrated and the residue was dissolved in AcOEt. This solution was washed with aqueous $NaHCO_3$ and brine, dried and evaporated to afford **15a** (95.0 mg: 95.0%)

***tert*-Butyl (5*S**,6*S**,7*S**)-7-Azido-5-chloro-2-hydroxy-8-oxo-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate 15b** A solution of **12** (333 mg) in 10% H_2O–acetone (5 ml) was treated with $AgBF_4$ (50% purity 390 mg) at −20 °C. The mixture was stirred at −20 °C for 2 h, then poured into ice-cooled $NaHCO_3$ solution. It was extracted with AcOEt, washed with H_2O, dried and evaporated. The residue was purified by column chromatography (SiO_2 20 g, *n*-hexane : AcOEt = 3 : 2) to obtain **15b** (195 mg: 62%) along with **15a** (33 mg: 11%). ^{1}H-NMR ($CDCl_3$) ppm: 6.28 (1H, dd, J = 10.1, 6.2 Hz), 5.66 (1H, d, J = 10.0 Hz), 4.81 (1H, d, J = 4.4 Hz), 4.59 (1H, dd, J = 6.2, 3.3 Hz), 4.01 (1H, dd, J = 4.4, 3.3 Hz), 1.51 (9H, s). IR ($CHCl_3$): 3500, 1795, 1743, 1725 (sh) cm^{-1}.

***tert*-Butyl (4*R**,5*R**,6*S**,7*S**)-7-Azido-5-bromo-4-hydroxy-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 17a *tert*-Butyl (6*S**,7*S**)-7-Azido-5-bromo-2-hydroxy-8-oxo-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate 17b** Method A (in H_2O–DME): 1,2-Dehydro-1-carbacephem **10** (160 mg) was dissolved in 25% H_2O–DME (10 ml). *N*-Bromosuccinimide (NBS) (120 mg) was added and the mixture was stirred at room temperature. After 3 h 20 min, further NBS (43 mg) was added and stirring was continued for 17 h 50 min. The mixture was then diluted with AcOEt, washed with brine, dried and concentrated. The residue was purified by column chromatography (SiO_2 20 g, *n*-hexane : AcOEt = 3 : 1) to obtain **17a** (21.3 mg: 9.7%) and **17b** (136 mg: 61.9%). **17a**; ^{1}H-NMR ($CDCl_3$) ppm: 6.3 (1H, d, J = 6 Hz), 5.1 (1H, d, J = 5 Hz), 4.6 (1H, dd, J = 6, 3 Hz), 4.4 (1H, m), 4.05 (1H, dd, J = 5, 2 Hz), 1.55 (9H, s). IR ($CHCl_3$): 2130, 1790, 1730, 1630 cm^{-1}. **17b**; ^{1}H-NMR ($CDCl_3$) ppm: 6.34 (1H, dd, J = 10.0, 6.6 Hz), 5.63 (1H, d, J = 10.0 Hz), 4.91 (1H, d, J = 5.1 Hz), 4.67 (1H, dd, J = 6.6, 3.4 Hz), 3.94 (1H, dd, J = 5.1, 3.4 Hz), 1.54 (9H, s). IR (KBr): 3350, 2130, 1760, 1750 cm^{-1}.

Method B (in Dimethylsulfoxide (DMSO)): H_2O (0.103 ml) and NBS (760 mg) were added to a solution of **10** (750 mg) in DMSO (45 ml). The mixture was stirred at room temperature for 5 h 30 min. Further NBS (250 mg) was added and stirring was continued for 18 h. It was then diluted with AcOEt, washed with brine, dried and evaporated. The residue was purified by column chromatography (SiO_2 70 g, *n*-hexane : AcOEt = 2 : 1) to afford **17a** (224 mg: 21.8%).

***tert*-Butyl (4*R**,5*R**,6*S**,7*S**)-7-Azido-4-hydroxy-5-iodo-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 18a and *tert*-Butyl (6*S**,7*S**)-7-Azido-2-hydroxy-5-iodo-8-oxo-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate 18b** Iodine (347 mg), KIO_3 (146 mg) and AcOH (0.4 ml) were added to a solution of **10** (300 mg) in a mixture of dioxane (2 ml) and H_2O (4 ml). The

mixture was stirred at 50 °C for 3 h. The red brown solution then was poured into ice-cooled aqueous $NaHCO_3$. It was extracted with AcOEt, washed with aqueous $NaHCO_3$ and brine, dried, and then evaporated. The residue was purified by column chromatography (SiO_2 15 g, *n*-hexane : AcOEt = 3 : 1) to give **18a** (101 mg: 22%) and **18b** (176 mg: 38%). **18a**; ^{1}H-NMR ($CDCl_3$) ppm: 6.24 (1H, d, J = 5 Hz), 5.11 (1H, d, J = 6 Hz), 4.71 (1H, m), 4.35 (1H, m), 3.51 (1H, m), 1.55 (9H, s). IR ($CHCl_3$): 2138, 1798, 1736 cm^{-1}. **18b**; ^{1}H-NMR ($CDCl_3$) ppm: 6.36 (1H, dd, J = 10, 1.8 Hz), 5.38 (1H, dd, J = 10, 2 Hz), 4.86 (1H, d, J = 4 Hz), 4.61 (1H, m), 4.11 (1H, dd, J = 9, 4 Hz), 1.47 (9H, s). IR ($CHCl_3$): 2130, 1798, 1795 (sh), 1750 cm^{-1}.

***tert*-Butyl (4*R**,5*S**,6*S**,7*S**)-7-Azido-4,5-dibromo-8-oxo-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylate 20** A 1 M solution of Br_2 in CCl_4 (1.8 ml) was added to a solution of **10** (200 mg) in CCl_4 (2 ml). The mixture was stirred at room temperature for 50 min. It was diluted with $CHCl_3$, washed with brine, dried and evaporated. The residue was chromatographed (SiO_2 15 g, *n*-hexane : AcOEt = 3 : 1) to give **20** (25.7 mg: 8.0%). ^{1}H-NMR ($CDCl_3$) ppm: 6.39 (1H, d, J = 6.0 Hz), 5.16 (1H, d, J = 4.7 Hz), 4.92 (1H, ddd, J = 6.0, 3.6, 0.7 Hz), 4.38 (1H, dd, J = 11.3, 4.7 Hz), 4.17 (1H, dd, J = 11.3, 3.6 Hz), 1.53 (9H, s). IR ($CHCl_3$): 2130, 1800, 1730, 1630 cm^{-1}.

***tert*-Butyl (4*R**,5*S**,6*S**,7*S**)-7-Azido-5-hydroxy-4-(*m*-chlorobenzoyloxy)-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 23a and *tert*-Butyl (4*R**,5*R**,6*S**,7*S**)-7-Azido-5-hydroxy-4-(*m*-chlorobenzoyloxy)-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 23b** A solution of **10** (259 mg) in CH_2Cl_2 (5 ml) was treated with *m*-chloroperbenzoic acid (*m*CPBA) (256 mg). The mixture was stirred at room temperature for 23 h. Further mCPBA (200 mg) was added and stirring was continued for 50 min. It was diluted with CH_2Cl_2, washed with 10% $Na_2S_2O_3$, saturated $NaHCO_3$ and brine. Evaporation after drying gave a residue, which was chromatographed (SiO_2 15 g, *n*-hexane : AcOEt = 5 : 1) to afford **23a** (9.0 mg: 2.1%) and **23b** (10.0 mg: 2.3%). **23a**; ^{1}H-NMR ($CDCl_3$) ppm: 7.26—7.99 (4H, m), 6.31 (1H, d, J = 5.6 Hz), 5.81 (1H, dd, J = 5.6, 3.8 Hz), 5.16 (1H, d, J = 4.8 Hz), 4.23 (1H, dd, J = 10.7, 3.8 Hz), 4.00 (1H, dd, J = 10.7, 4.8 Hz), 1.54 (9H, s). IR ($CHCl_3$): 2130, 1795, 1735 cm^{-1}. **23b**; ^{1}H-NMR ($CDCl_3$) ppm: 7.31—7.98 (4H, m), 6.35 (1H, d, J = 5.1 Hz), 5.52 (1H, dd, J = 5.1, 2.3 Hz), 5.16 (1H, d, J = 5.6 Hz), 4.36 (1H, m), 3.94 (1H, dd, J = 5.6, 1.6 Hz), 1.55 (9H, s). IR ($CHCl_3$): 2130, 1795, 1730 cm^{-1}.

***tert*-Butyl (4*S**,5*S**,6*S**,7*S**)-7-Amino-4,5-dihydroxy-8-oxo-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylate 24a** A solution of **4a** (45 mg) in EtOH (3.8 ml) was stirred with 10% Pd–C (23 mg) at room temperature under a stream of H_2 for 2 h 40 min. The catalyst was filtered off and the filtrate was concentrated to give **24a** (39.4 mg: 96.0%). IR ($CHCl_3$): 3400, 1790, 1730, 1640 cm^{-1}.

(4*S,5*S**,6*S**,7*S**)-2-Carboxy-4,5-dihydroxy-8-oxo-1-azabicyclo[4.2.0]-oct-2-ene-7-ammonium Trifluoroacetate 25a** A solution of the ester **24a** (115 mg) in a mixture of CH_2Cl_2 (2.4 ml) and CF_3CO_2H (0.8 ml) was stirred at room temperature for 1 h 50 min. The mixture was concentrated then suspended in ether. A precipitate was filtered off and dried to give **25a** (65.2 mg: 46.7%). IR (KBr): 1785, 1680, 1630 cm^{-1}.

(4*S,5*S**,6*S**,7*S**)-7-[2-(2-Amino-4-thiazolyl)-2-(*Z*)-methoxyiminoacetamido]-4,5-dihydroxy-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid 27a** NEt_3 (0.019 ml) and PCl_5 (29 mg) were added to a solution of 2-(2-tritylamino-4-thiazolyl)-2-(*Z*)-methoxyiminoacetic acid (57 mg) in CH_2Cl_2 (2 ml). The mixture was stirred at room temperature for 50 min. After addition of *n*-hexane (3.5 ml) with stirring, a supernatant was removed by decantation. The residue, 2-(2-tritylamino-4-thiazolyl)-2-(*Z*)-methoxyiminoacetyl chloride, was dissolved in THF (1.8 ml). This solution was added to a solution of **25a** (38 mg) and NEt_3 (0.053 ml) in 50% aqueous THF (1.8 ml) under ice-cooling. The mixture was stirred for 2 h 55 min, then the same amount of 2-(2-tritylamino-4-thiazolyl)-2-(*Z*)-methoxyiminoacetyl chloride in THF (1.8 ml) was further added and stirring was continued for 1 h 15 min. The reaction mixture was acidified with 1 N HCl and extracted with AcOEt three times. The combined extracts were dried and evaporated to give a residue (**26a**). The residue was dissolved in 50% AcOH–H_2O and the mixture was heated at 55 °C for 30 min. Then AcOEt and H_2O were added, and the aqueous layer was separated and concentrated. The residue was subjected to chromatography (Diaion HP-20 10 ml, H_2O : MeOH = 4 : 1—1 : 1) to afford **27a** (12.0 mg: 29.6%). ^{1}H-NMR (CD_3OD) ppm: 7.06 (1H, br), 6.22 (1H, m), 5.42 (1H, d, J = 4.2 Hz), 4.37 (1H, m), 3.96 (3H, s), 3.60—4.16 (2H, m). IR (KBr): 3300—3400, 1780 (sh), 1770, 1640—1670 cm^{-1}.

***tert*-Butyl (4*R**,5*R**,6*S**,7*S**)-7-Amino-5-chloro-4-hydroxy-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 24b** A solution of **15a** (68 mg) in EtOH (1.6 ml) was stirred with 10% Pd–C (28 mg) and *p*-TsOH (36 mg) at room temperature under a stream of H_2 for 45 min, then filtered to remove the catalyst. The filtrate was concentrated to give a residue, which was dissolved in $CHCl_3$. The solution was washed with aqueous $NaHCO_3$, dried and evaporated to afford **24b** (49 mg, 78.5%). ^{1}H-NMR ($CDCl_3$) ppm: 6.21 (1H, dd, J = 5.1, 1.0 Hz), 4.66 (1H, d, J = 4.9 Hz), 4.28—4.44 (2H, m), 4.10 (1H, dd, J = 4.9, 1.1 Hz), 1.53 (9H, s). IR ($CHCl_3$): 1800 (sh), 1790, 1780, 1740, 1640 cm^{-1}.

(4*R,5*R**,6*S**,7*S**)-7-[2-(2-Amino-4-thiazolyl)-2-(*Z*)-methoxyiminoacetamido]-5-chloro-4-hydroxy-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid 27b** A solution of the ester **24b** (49 mg) in 50% TFA–CH_2Cl_2 (3 ml) was stirred at 0 °C to room temperature for 1 h 20 min, then concentrated to give a residue. The residue was taken up in benzene and the solution was concentrated to afford crude **25b** (54 mg). This was redissolved in 50% THF–H_2O (2 ml), and 2-(2-tritylamino-4-thiazolyl)-2-(*Z*)-methoxyiminoacetyl chloride in THF (1.2 ml) {prepared from 2-(2-tritylamino-4-thiazolyl)-2-(*Z*)-methoxyiminoacetic acid (88.6 mg), PCl_5 (42 mg) and NEt_3 (0.028 ml)} was added under ice-cooling. The mixture was stirred for 2 h 30 min. After addition of 0.5 N HCl (3 ml) the mixture was extracted with AcOEt, dried and evaporated. The residue was dissolved in 50% AcOH–H_2O (6 ml) and the solution was heated at 55 °C for 1 h 30 min with stirring. The mixture was concentrated and the residue was purified by column chromatography (Diaion HP-20AG 15 ml, H_2O : MeOH = 10 : 1—2 : 1) to afford **27b** (6.0 mg: 8.5%). ^{1}H-NMR (CD_3OD–D_2O) ppm: 6.89 (1H, br s), 6.15 (1H, br d, J = 4.4 Hz), 5.75 (1H, d, J = 4.2 Hz), 4.38 (3H, m), 4.00 (3H, s). IR (KBr): 3450, 1788 (sh), 1777, 1768, 1758 (sh), 1678, 1668 cm^{-1}.

***tert*-Butyl (4*R**,5*R**,6*S**,7*S**)-7-Amino-5-bromo-4-hydroxy-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 24c** In the same manner as described for **24b**, the azide **17a** (170 mg) afforded the amine **24c** (87 mg: 55.2%).

(4*R,5*R**,6*S**,7*S**)-5-Bromo-2-carboxy-4-hydroxy-8-oxo-1-azabicyclo-[4.2.0]oct-2-ene-7-ammonium Trifluoroacetate 25c** A solution of the ester **24c** (80 mg) in 50% TFA–CH_2Cl_2 (1 ml) was stirred at room temperature for 1 h. The mixture was concentrated to give a residue. The residue was taken up in benzene, and the mixture was concentrated again. Ether was added, then the suspension was filtered and the solid was dried to afford **25c** (70 mg: 67.8%).

(4*R,5*R**,6*S**,7*S**)-7-[2-(2-Amino-4-thiazolyl)-2-(*Z*)-methoxyiminoacetamido]-5-bromo-4-hydroxy-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid 27c** 2-(2-Tritylamino-4-thiazolyl)-2-(*Z*)-methoxyiminoacetyl chloride in THF (2 ml), prepared from the corresponding carboxylic acid (79 mg) and PCl_5 (37 mg), was added to a solution of **25c** (63 mg) and NEt_3 (0.010 ml) in 50% THF–H_2O (2 ml) under ice-cooling. To the mixture, NEt_3 was added to maintain the pH at 7—8. Stirring was continued at 0 °C for 2 h, then 1 N HCl was added to adjust the pH at 2. The mixture was extracted with AcOEt twice, and the combined extract was dried and evaporated. The residue was dissolved in 50% AcOH–H_2O (10 ml) and this solution was heated at 50 °C for 40 min. The mixture was concentrated and the residue was suspended in a mixture of MeOH and ether. The precipitate was filtered off and dried to give crude **27c**, which was purified by column chromatography (Diaion HP-20AG, 30 ml, H_2O : MeOH = 1 : 0—2 : 1) to afford **27c** (49 mg: 53.0%). ^{1}H-NMR (CD_3OD–H_2O) ppm: 6.91 (1H, s), 6.25 (1H, d, J = 4.8 Hz), 5.76 (1H, d, J = 4.5 Hz), 4.02—4.53 (3H, m), 3.97 (3H, s).

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