SYNTHESES AND BIOLOGICAL ACTIVITIES OF NEW CARBAPENEM DERIVATIVES

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3-β-Alanyloxymethyl, 3-glycyloxymethyl and 3-methyl derivatives of 6-(1-hydroxyethyl)-carbapenems, (**VIIa, VIIb** and **VIII**), and 3-methyl-6-(1-hydroxyethyl)carbapenam (**IX**) were synthesized from 3-(1-*tert*-butyldimethylsilyloxyethyl)-4-(3-chloro-2-oxopropyl)-2-azetidinone (**I**). The antibacterial activities of these compounds proved that the Δ^2 double bond was essential for the appearance of bioactivity, whereas the amino group on the C-3 side chain was not necessary.

Thienamycin[1], as first reported in 1976, is a novel carbapen-2-em antibiotic possessing a 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid nucleus with a 1-hydroxyethyl group at C-6 and a cysteamine side chain at C-3. It is different from the traditional β-lactam antibiotics, namely the penicillins and the cephalosporins, in that it has no amide functionality. Thienamycin has a broad spectrum of potent antibacterial activity[2], and is stable to bacterial β-lactamases. That encouraged many medicinal chemists to synthesize congeners of thienamycin and to examine their activities against many different bacteria. As a result, many carbapenem congeners were synthesized all over the world, and several new compounds may still be under development.

In a search for more active analogues of the carbapenems, we synthesized **VIIa, VIIb** and **VIII**, which are novel C-3 substituted derivatives of the carbapenems. We wish now to report the synthetic route and the antibiotic activities of these derivatives.

Chemistry

As a starting material, we chose optically active 3-(1-*tert*-butyldimethylsilyloxyethyl)-4-(3-chloro-2-oxopropyl)-2-azetidinone (**I**) obtained from L-threonine according to a method recently developed in our laboratories[3]. Treatment of **I** with glycine or β-alanine, in which the amino function was protected by a *p*-nitrobenzyloxycarbonyl group, or with formic acid in DMF by use of Et_3N as a base gave esters **IIa, IIb** or **IIc** (mp 87~88°C) in 56%, 52% or 75% yield, respectively. According to the usual method, these compounds were converted to the 1-triphenylphosphoranylidenemethyl compounds (**Va, Vb** and **Vc**) for the intramolecular WITTIG reaction[4,5]. That is, addition of *p*-nitrobenzyl glyoxylate to **IIa, IIb** or **IIc** afforded a corresponding mixture of diastereoisomers, **IIIa, IIIb** or **IIIc**. Chlorination of **IIIa, IIIb** or **IIIc** with thionyl chloride, and successive phosphoranylidenation with triphenylphosphine-lutidine gave **IVa, IVb** or **IVc**, in 58%, 66% or 59% yield, respectively. In the case of **IIIc**, the cyclized compound (**VIc'**) was found to be unstable under the conditions of desilylation with Bu_4NF - AcOH in THF. Desilylation of **IVa, IVb** and **IVc** in MeOH with 10% aqueous HCl gave **Va, Vb** and **Vc** in 82%, 81% and 98% yields, respectively, which easily cyclized in boiling benzene to give **VIa, VIb** and **VIc** in 94%, 77% and 88% yields, respectively. Hydrogenation of **VIa** and **VIb** with 10% palladium on carbon in THF - 0.1 M phosphate buffer for 4 minutes under 1 atm pressure at room temperature gave

Chart 1.

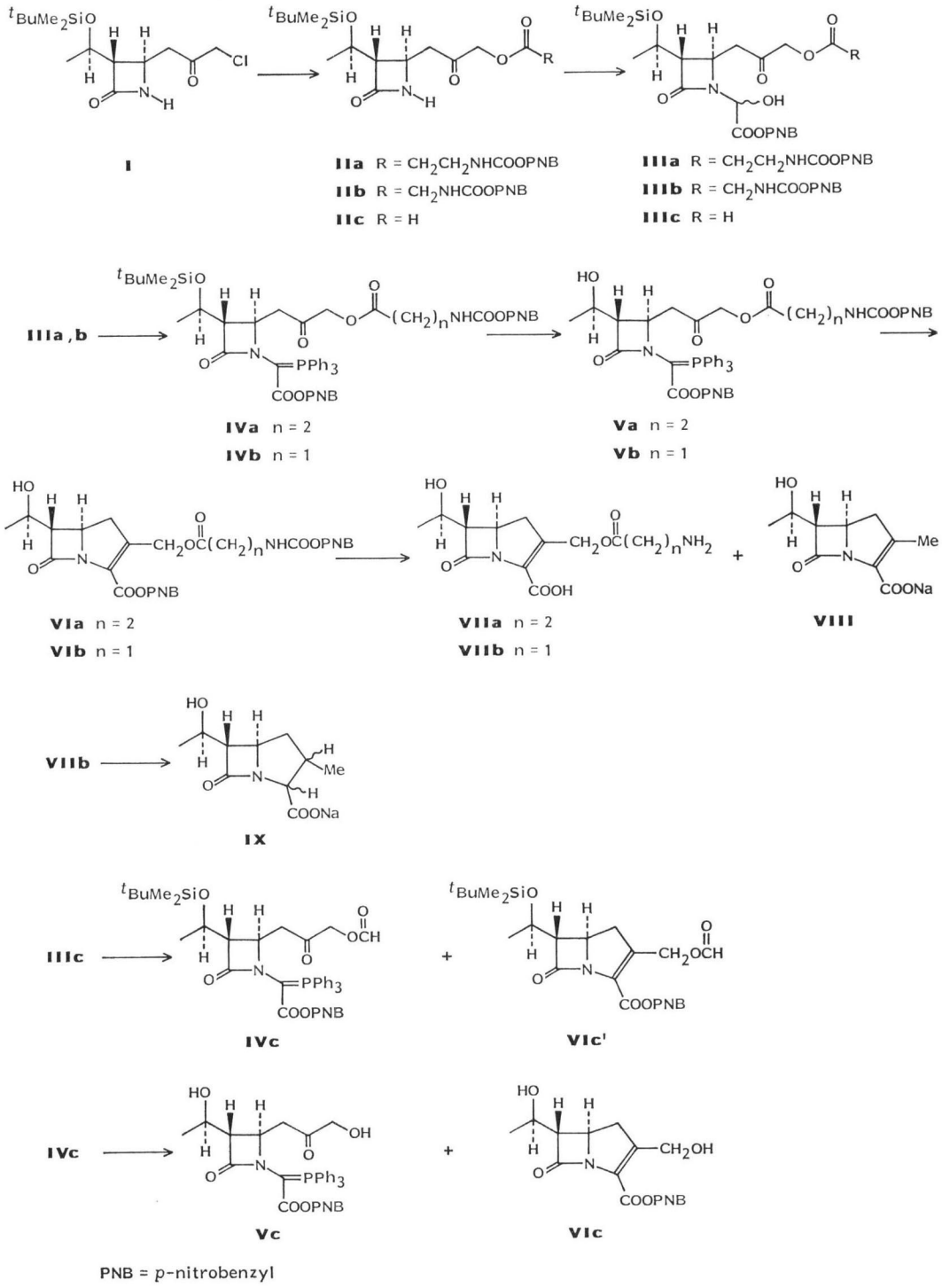
tBuMe2SiO
Cl
I
IIa R = CH2CH2NHCOOPNB
IIb R = CH2NHCOOPNB
IIc R = H
IIIa R = CH2CH2NHCOOPNB
IIIb R = CH2NHCOOPNB
IIIc R = H
IIIa,b
(CH2)nNHCOOPNB
PPh3
COOPNB
IVa n = 2
IVb n = 1
Va n = 2
Vb n = 1
CH2OC(CH2)nNHCOOPNB
VIa n = 2
VIb n = 1
CH2OC(CH2)nNH2
COOH
VIIa n = 2
VIIb n = 1
Me
COONa
VIII
IX
IIIc
OCH
IVc
VIc'
CH2OCH
OH
Vc
VIc
CH2OH
PNB = p-nitrobenzyl

Table 1. The MIC of compounds **VIIa, VIIb, VIII** and **IX**.

Organism	MIC (μg/ml)			
	VIIa	**VIIb**	**VIII**	**IX**
Staphylococcus aureus 209P	0.02	0.1	0.1	>200
S. aureus 56	0.1	0.2	0.2	>200
Escherichia coli NIHJ	0.4	0.8	0.4	>200
E. coli 609	0.4	0.8	0.8	>200
Shigella flexneri 2a	0.4	0.8	0.8	>200
Salmonella enteritidis G.	0.8	0.8	0.8	>200
Klebsiella pneumoniae 806	0.4	0.8	0.8	>200
Klebsiella sp. 846	0.4	0.8	0.4	>200
Proteus vulgaris	3.1	1.5	3.1	>200
Pseudomonas aeruginosa	25	25	25	>200

VIIa and **VIIb** in 25% and 36% yields, respectively, accompanied by a more hydrogenolized by-product (**VIII**) in 47% and 15% yields, respectively. The compound **VIc**, however, did not yield the expected carbapen-2-em product under the same conditions. Hydrogenation of **VIb** under more drastic conditions (2.5 atm pressure for 30 minutes) gave a carbapenam compound (**IX**) in 40% yield.

Thus we accomplished the syntheses of new 3-aminoacyloxymethyl and 3-methyl carbapenems. It should be noted that the compounds **VIIa** and **VIIb** were extremely unstable in high aqueous concentration.

Antibacterial Activity

The minimum inhibitory concentrations (MIC) of **VIIa, VIIb, VIII** and **IX** against various organisms are listed in Table 1. These results show that the Δ^2 double bond is essential for the appearance of biological activities, but that the amino group on the C-3 side chain is not necessary.

Experimental

^{1}H NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer using Me_4Si as an internal standard. The IR spectra were determined on a Jasco IR A-2 spectrometer. Preparative TLC was performed on silica gel plates (Merck 60 PF_{254}).

[3*S*-[3α(*S**),4β]]-3-(1-*tert*-Butyldimethylsilyloxyethyl)-4-[3′-(3″-*p*-nitrobenzyloxycarbonylaminopropionoxy)-2′-oxopropyl]-2-azetidinone (**IIa**)

A mixture of **I** (3.17 g, 10 mmol), *N*-*p*-nitrobenzyloxycarbonyl-β-alanine (4.0 g, 15 mmol), Et_3N (2.0 g, 20 mmol) and NaI (6 g) in DMF (90 ml) was stirred for 18 hours at room temperature, diluted with EtOAc, washed with 5% aqueous HCl, water, satd $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue which was purified on a silica gel (150 g) column. Elution with EtOAc gave **IIa** (3.1 g, 56%) as a viscous oil; ^{1}H NMR ($CDCl_3$) δ 0.07 (6H, s), 0.88 (9H, s), 1.21 (3H, d, J=6 Hz), 2.5~2.9 (5H, m, C_3-H, C_4-CH_2CO, $OCOCH_2$), 3.30~3.75 (2H, m, $CH_2NHCOOPNB$), 3.75~4.4 (2H, m, C_4-H, C_3-H), 4.68 (2H, s, $COCH_2OCO$), 5.17 (2H, s, $COOCH_2Ar$), 5.55 (1H, broad, NH), 6.13 (1H, bs, NH), 7.46 (2H, d, J=9 Hz), 8.17 (2H, d, J=9 Hz).

[3*S*-[3α(*S**),4β]]-3-(1-*tert*-Butyldimethylsilyloxyethyl)-4-(3′-*p*-nitrobenzyloxycarbonylaminoacetoxy-2′-oxopropyl)-2-azetidinone (**IIb**)

Treatment of **I** with *N*-*p*-nitrobenzyloxycarbonylglycine in the same manner as described above gave **IIb** (52%) as a viscous oil; ^{1}H NMR ($CDCl_3$) δ 0.05 (6H, s), 0.86 (9H, s), 1.20 (3H, d, J=6 Hz), 2.4~3.2 (3H, m, C_3-H, C_4-CH_2CO), 3.8~4.4 [4H, m, C_4-H, C_3-H, CH_2NH as a doublet (J=6 Hz) at δ 4.10], 4.72 (2H, s, $COCH_2OCO$), 5.20 (2H, s, CH_2Ar), 5.80 (1H, t, J=6 Hz, $CH_2NHCOOPNB$), 6.40 (1H, bs, NH), 7.48 (2H, d, J=9 Hz), 8.16 (2H, d, J=9 Hz).

[3*S*-[3α(*S**),4β]]-3-(1-*tert*-Butyldimethylsilyloxyethyl)-4-(3′-formyloxy-2′-oxopropyl)-2-azetidinone (**IIc**)

Treatment of **I** with formic acid in a similar way as described for the formation of **IIa** gave **IIc** (75%) as a crystalline solid; mp 87~88°C; IR ν_{max} (Nujol) 3150, 1775, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.86 (9H, s), 1.20 (3H, d, J=6 Hz), 2.5~3.1 (3H, m, C_3-H, C_4-CH_2CO), 3.8~4.4 (2H, m, C_4-H, C_3-CH), 4.70 (2H, s, $COCH_2OCHO$), 6.26 (1H, bs, NH), 8.07 (1H, s, CHO).

A Mixture of [3*S*-[3α(*S**),4β,1(*R**)]]- and [3*S*-[3α(*S**),4β,1(*S**)]]-1-(1-Hydroxy-1-*p*-nitrobenzyloxycarbonylmethyl)-3-(1-*tert*-butyldimethylsilyloxyethyl)-4-[3′-(3″-*p*-nitrobenzyloxycarbonylaminopropionoxy)-2′-oxopropyl]-2-azetidinone (**IIIa**)

A solution of *p*-nitrobenzyl glyoxylate monohydrate (712 mg, 3.13 mmol) in benzene (120 ml) was concentrated to about half the volume at reflux temperature to remove the water azeotropically. To this concentrate was added a solution of **IIa** (865 mg, 1.57 mmol) in benzene (20 ml), the resulting solution was concentrated to about 40 ml, refluxed for 8~15 hours, and then concentrated *in vacuo* to give an oily mixture which was separated on a silica gel column. Elution with *i*-Pr_2O - EtOAc (2: 1) recovered the starting glyoxylate, and elution with EtOAc gave **IIIa** (502 mg, 42%) as a gummy mixture of diastereoisomers, which was employed for the next reaction. ^1H NMR ($CDCl_3$) δ 0.02 and 0.04 (3H, each singlet), 0.79 and 0.83 (9H, each singlet), 1.10 and 1.19 (3H, each doublet, J=6 Hz), 2.47~3.03 (5H, m, C_4-CH_2, $OCOCH_2$, C_3-H), 3.28~3.78 (2H, m, CH_2NH), 3.78~4.90 (6H, m, C_4-H, OH, NH, C_3-H, $COCH_2OCO$), 5.17~5.38 (4H, m, $COOCH_2Ar\times2$), 5.62 (1H, m, NC*H*(OH)), 7.35~7.70 (4H, broad doublet, aromatic), 8.1~8.35 (4H, broad doublet, aromatic).

A Mixture of [3*S*-[3α(*S**),4β,1(*R**)]]- and [3*S*-[3α(*S**),4β,1(*S**)]]-1-(1-Hydroxy-1-*p*-nitrobenzyloxycarbonylmethyl)-3-(1-*tert*-butyldimethylsilyloxyethyl)-4-(3′-*p*-nitrobenzyloxycarbonylaminoacetoxy-2′-oxopropyl)-2-azetidinone (**IIIb**)

Treatment of **IIb** (780 mg, 1.44 mmol) with *p*-nitrobenzyl glyoxylate monohydrate (650 mg, 2.88 mmol) as described above gave **IIIb** (860 mg, 80%) as a gummy mixture of diastereoisomers; ^1H NMR ($CDCl_3$) δ 0.03 (6H, s), 0.84 and 0.87 (9H, each singlet), 1.13 and 1.23 (3H, each doublet, J=5 Hz), 2.8~3.1 (2H+1H, m, C_3-H, C_4-CH_2CO), 3.9~4.5 (4H, m, C_3-CH, C_4-H, $OCOCH_2NH$), 4.74 (2H, bs, $COCH_2OCO$), 5.15~5.70 (6H, m, $COOCH_2Ar\times2$, NC*H*(OH), NHCOO), 7.4~7.7 (4H, m, aromatic), 8.25 (4H, d, J=8 Hz, aromatic).

A Mixture of [3*S*-[3α(*S**),4β,1(*R**)]]- and [3*S*-[3α(*S**),4β,1(*S**)]]-1-(1-Hydroxy-1-*p*-nitrobenzyloxycarbonylmethyl)-3-(1-*tert*-butyldimethylsilyloxyethyl)-4-(3′-formyloxy-2′-oxopropyl)-2-azetidinone (**IIIc**)

Treatment of **IIc** (623 mg, 1.89 mmol) with *p*-nitrobenzyl glyoxylate monohydrate (859 mg, 3.78 mmol) as described above gave a crude oily mixture which was chromatographed on a silica gel (50 g) column. Elution with *i*-Pr_2O - EtOAc (4: 1) gave **IIIc** (770 mg, 75.6%) as a gummy mixture of diastereoisomers; IR ν_{max} (film) 3450, 1740, 1610 cm^{-1}; ^1H NMR (acetone-d_6) δ 0.02 (3H, s), 0.06 (3H, m, C_3-H, C_4-CH_2CO), 3.9~4.5 (2H, m, C_4-H, C_3-H), 4.79 and 4.82 (2H, each singlet, $COCH_2OCO$), 5.28 and 5.32 (2H, each singlet, $COOCH_2Ar$), 5.57 (1H, bs, N-C*H*(OH)), 7.5~8.3 (5H, m, aromatic, OCHO).

[3*S*-[3α(*S**),4β]]-1-(1-*p*-Nitrobenzyloxycarbonyl-1-triphenylphosphoranylidenemethyl)-3-(1-*tert*-butyldimethylsilyloxyethyl)-4-[3′-(3″-*p*-nitrobenzyloxycarbonylaminopropionoxy)-2′-oxopropyl]-2-azetidinone (**IVa**)

To a stirred solution of **IIIa** (490 mg, 0.64 mmol) in THF (15 ml) was added 2,6-lutidine (214 mg, 2.0 mmol) and thionyl chloride (238 mg, 0.146 ml, 2.0 mmol) at −25°C. After stirring for 20 minutes at −20°C, the reaction mixture was filtered to remove lutidine hydrochloride, which was washed with a small amount of THF. The combined filtrate was concentrated *in vacuo* at room temperature to give an oily residue, to which dry benzene (10 ml) was added and evaporated *in vacuo* (this operation was repeated three times). The residual oil was dissolved in THF (15 ml), and to this solution was added triphenylphosphine (340 mg, 1.28 mmol) and 2,6-lutidine (274 mg, 1.28 mmol). The mixture was stirred for 4 hours at 45°C, diluted with EtOAc, washed with brine, dried over $MgSO_4$, and evaporated to give a gummy residue which was chromatographed on a silica gel (20 g) column. Elution with benzene - EtOAc (1: 2) gave **IVa** (371 mg, 57.5%) as a gum which was employed for the next reaction.

[3*S*-[3α(*S**),4β]]-1-(1-*p*-Nitrobenzyloxycarbonyl-1-triphenylphosphoranylidenemethyl)-3-(1-*tert*-butyldimethylsilyloxyethyl)-4-(3′-*p*-nitrobenzyloxycarbonylaminoacetoxy-2′-oxopropyl)-2-azetidinone (**IVb**)

Treatment of **IIIb** in the same manner as described above for the preparation of **IVa** from **IIIa** gave **IVb** (66.5%) as a gum which was employed for the next reaction.

[3*S*-[3α(*S**),4β]]-1-(1-*p*-Nitrobenzyloxycarbonyl-1-triphenylphosphoranylidenemethyl)-3-(1-*tert*-butyldimethylsilyloxyethyl)-4-(3′-formyloxy-2-oxopropyl)-2-azetidinone (**IVc**) and *p*-Nitrobenzyl [5*R*-[5α,6α(*R**)]]-3-(Formyloxymethyl)-6-(1-*tert*-butyldimethylsilyloxyethyl)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**VIc′**)

Treatment of **IIIc** (770 mg, 1.43 mmol) with 2,6-lutidine (460 mg, 4.29 mmol) and $SOCl_2$ (510 mg, 4.29 mmol), and successively with triphenylphosphine (750 mg, 2.86 mmol) and 2,6-lutidine (306 mg, 2.86 mmol) in the same way as described above for the preparation of **IVa** gave a crude mixture which was chromatographed on a silica gel (100 g) column. Elution with benzene - acetone (17: 3) gave **VIc′** (Rf 0.70, 80 mg, 11%); ^{1}H NMR ($CDCl_3$) δ 0.10 (6H, s), 0.88 (9H, s), 1.25 (3H, d, J=6 Hz), 2.8~3.3 (2H, m, C_4-H_2CO), 4.05~4.45 (2H, m, C_5-H, C_6-H), 4.9~5.6 (4H, m, $COOCH_2Ar$, C_3-CH_2OCHO), 7.63 (2H, d, J=9 Hz), 8.08 (1H, s, CHO), 8.20 (2H, d, J=9 Hz); and **IVc** (656 mg, 58.6%) which was employed for the next reaction.

Desilylation of **IVa**, **IVb** and **IVc**

To a stirred solution of **IVa** (1.005 g, 1 mmol) in MeOH (100 ml) was added 10% aqueous HCl solution (50 ml) at 0°C. After stirring for 1 hour at room temperature, the reaction mixture was ice-cooled and the pH adjusted to 8 by the addition of satd $NaHCO_3$. The mixture was extracted with EtOAc. The extract was then washed with brine, dried over Na_2SO_4, and concentrated after suction filtration to give an oily residue which was chromatographed on a silica gel (90 g) column. Elution with cyclohexane - acetone (7: 13) gave **Va** (739 mg, 82%) which was employed for the next reaction without further purification. A similar treatment of **IVb** and **IVc** gave **Vb** and **Vc** in 81.4% and 98% yields, respectively, which were employed for the next reactions. IR of **Vb**; ν_{max} ($CHCl_3$) 1740, 1630, 1608, 1520 cm^{-1}.

p-Nitrobenzyl [5*R*-[5α,6α(*R**)]]-3-(3′-*p*-Nitrobenzyloxycarbonylaminopropionoxymethyl)-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**VIa**)

A solution of **Va** (739 mg, 0.83 mmol) in benzene (150 ml) containing 2 mg of hydroquinone was concentrated to a volume of 80 ml at boiling temperature, and then refluxed for 2 hours. After evaporation of benzene *in vacuo*, the residue was chromatographed on a silica gel (30 g) column. Elution with cyclohexane - acetone (2: 3) gave **VIa** (478 mg, 94%) as a powder; IR ν_{max} (Nujol) 1775, 1745, 1715, 1694 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 1.25 (3H, d, J=6 Hz), 2.5~3.8 (8H, m), 3.9~4.5 (3H, m), 5.06 (1H, m), 5.19 (2H, s), 5.25, 5.53 (2H, AB-q, J=14 Hz), 6.55 (1H, bs, NH), 7.50~8.27 (8H, m).

p-Nitrobenzyl [5*R*-[5α,6α(*R**)]]-3-(*p*-Nitrobenzyloxycarbonylaminoacetoxymethyl)-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**VIb**)

A solution of **Vb** (540 mg, 0.616 mmol) in benzene was treated as described above to give **VIb** (238 mg, 76.7%) as a powder; IR ν_{max} ($CHCl_3$) 1780, 1730, 1605, 1520 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, d, J=6 Hz), 2.6~3.4 (4H, m, C_4-H_2, C_6-H, OH), 3.9~4.5 (4H, m, $OCOCH_2NH$, C_5-H, C_6-H), 5.0~5.7 (6H, m, $COOCH_2\times2$, C_3-CH_2OCO), 7.65 (4H, d, J=8 Hz), 7.4~7.6 (1H, m, NH), 8.25 (4H, d, J=8 Hz).

p-Nitrobenzyl [5*R*-[5α,6α(*R**)]]-3-Hydroxymethyl-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (**VIc**)

A solution of **Vc** (450 mg, 0.702 mmol) in benzene was treated as described above. Chromatography on a silica gel column (eluent: EtOAc) gave **VIc** (223 mg, 87.5%); Rf 0.46 (EtOAc); ^{1}H NMR (acetone-d_6) δ 1.26 (3H, d, J=6 Hz), 2.9~3.3 (3H, m, C_4-H_2, C_6-H), 4.0~4.7 (6H, m, C_3-H_2, C_5-H, C_6-H, OH$\times$2), 5.22, 5.53 (2H, AB-q, J=14 Hz, $COOCH_2Ar$), 7.63 (2H, d, J=8.5 Hz), 8.20 (2H, d, J=8.5 Hz).

[5*R*-[5α,6α(*R**)]]-3-(3-Aminopropionoxymethyl)-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**VIIa**) and Sodium [5*R*-[5α,6α(*R**)]]-3-Methyl-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**VIII**)

A mixture of **VIa** (56 mg, 0.0914 mmol) and 10% Pd-C (28 mg) in THF (4 ml) and 0.1 M phosphate buffer [0.1 M $Na_2HPO_4 \cdot 12H_2O$ - 0.1 M $NaH_2PO_4 \cdot 2H_2O$ (7: 4), 4 ml] was hydrogenated at room temperature and 1 atm pressure for 4 minutes with vigorous stirring. The reaction mixture was filtered through Celite, and the remaining Pd-C was washed with 0.1 M phosphate buffer (3 ml×2). The combined filtrate was washed with Et_2O (3 ml×2) and concentrated *in vacuo* at 20°C to a volume of 2 ml. The residual aqueous mixture was separated on a high porous polymer column (Mitsubishi Chemical Industries Ltd., CHP 20P, wet 20 ml). Elution with cold water and successive freeze drying gave **VIII** (10 mg, 47%) as a pale yellow powder; ^{1}H NMR (D_2O) δ 1.37 (3H, d, J=6 Hz), 2.08 (3H, t, J=0.5 Hz, C_3-CH_3), 2.84, 3.00 (2H, each multiplet, C_4-H_2), 3.37 (1H, dd, J=2, 6 Hz, C_6-H), 3.95~4.45 (2H, m, C_5-H, C_6-CH); and **VIIa** (6.9 mg, 25.3%) as a white powder; ^{1}H NMR (D_2O) δ 1.35 (3H, d, J=6 Hz), 2.7~3.15 (4H, m, C_4-H_2 and OCOCH_2CH$_2$N), 3.25~3.6 (3H, m, C_6-H and CH_2N), 3.8~4.5 (2H, m, C_5-H and C_6-H), 4.97, 5.35 (2H, AB-q, J=13 Hz, C_3-CH_2OCO), which turned to purple-red on spraying with ninhydrin.

[5*R*-[5α,6α(*R**)]]-3-(Aminoacetoxymethyl)-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (**VIIb**) and its Hydrogenolyzed Sodium Salt (**VIII**)

Compound **VIb** (185 mg, 0.309 mmol) was treated as described above to give **VIIb** (31.5 mg, 35.8%) as a white powder; ^{1}H NMR (D_2O) δ 1.36 (3H, d, J=6 Hz), 2.8~3.2 (2H, m, C_4-H_2), 3.3~3.7 (1H, m, C_6-H), 4.0~4.5 (4H, m, $OCOCH_2N$, C_5-H and C_6-CH), 5.05, 5.45 (2H, AB-q, J=13 Hz, C_3-CH_2); and **VIII** (11 mg, 15.3%).

Sodium [2ξ,3ξ,5*R*,6*S*,8*R*]-3-Methyl-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (**IX**)

A mixture of **VIb** (227 mg, 0.379 mmol) and 10% Pd on carbon (680 mg) in THF (15 ml) and 0.1 M phosphate buffer [0.1 M $Na_2HPO_4 \cdot 12H_2O$ - 0.1 M $NaH_2PO_4 \cdot 2H_2O$ (7: 4), 15 ml] was hydrogenated at room temperature and 2.4 atm pressure for 30 minutes. The reaction mixture was filtered on Celite, and the remaining Pd-C was washed with 0.1 M phosphate buffer (20 ml). The combined filtrate was washed with Et_2O (10 ml×3) and concentrated *in vacuo* at 20°C to a volume of 10 ml. The residual aqueous mixture was separated on a high porous polymer (Mitsubishi Chemical Ind. Ltd., CPH 20P, wet 80 ml) column. Elution with cold water and successive freeze drying gave **IX** (36 mg, 40.4%) as a white powder; ^{1}H NMR (D_2O) δ 1.24 (3H, d, J=6 Hz), 1.44 (3H, d, J=6 Hz), 1.6~2.5 (2H, m, C_4-H_2), 2.6~3.5 [2H, m, C_3-H and containing 1H at δ 3.34 (dd, J=2, 6 Hz, C_6-H)], 3.7~4.6 [3H, m, C_5-H, C_3-H and containing 1H at δ 3.94 (d, J=8 Hz)].

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