SYNTHESIS AND BIOLOGICAL PROPERTIES OF 1-OXAPENEMS†

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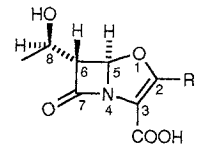
Several 2-substituted oxapenems, **1a**, **1b** and **1c**, bearing the hydroxyethyl side-chain at 6α were synthesized in a highly stereoselective manner starting from the commercially available 3α-hydroxyethyl-4β-acetoxyazetidinone (**5**). The stability, *in vitro* antibacterial activity, and β-lactamase inhibitory properties of these oxapenems were examined. The 2-isopropyl penem **1c** had considerable stability as shown by its $t_{1/2}$ of 200 minutes in pH 7.0 buffer solution and at 37°C, while the other two **1a** and **1b** were labile. Interestingly, the antibacterial activity of these compounds paralleled their stability and thus penem **1c** showed appreciable MICs, whereas the other two were virtually inactive. All three penems inhibited certain cephalosporinases strongly, but penicillinases only weakly. Thus, the inhibitory spectrum was similar to that for *epi*-thienamycin B and not the spectrum for clavulanic acid.

In continuing our studies on 1-oxanuclear analogs of cephalosporins and cephamycins, we were interested in synthesizing oxapenems (**1**) with the thienamycin-type hydroxyethyl side-chain and in determining their antibacterial activity. While one might expect high antibacterial activity from oxapenems (**1**) on the basis of their structural similarity to carbapenems and penems, difficulties were anticipated in synthesizing the oxapenem nucleus which was presumed to be very fragile because of high ring-strain and the presence of an electronegative oxygen atom at position 1. Moreover, even if an oxapenem compound could be synthesized, the question still remained of whether or not it would be stable enough to tolerate antibacterial testing. Nevertheless, we expected that the 6α-1′-hydroxyethyl side-chain would stabilize the oxapenem nucleus as is the case with the carbapenem and penem nuclei[3~5] and that certain substituents at the 2 position would favor nucleus stabilization for steric and electronic reasons. With these expectations in mind, we undertook the synthesis.

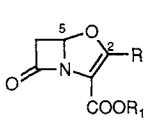


1

Chemistry

At the time we started our work, only a few studies had been reported on the synthesis of oxapenem derivatives. Most of the synthesized derivatives were unsubstituted at the 6 position as depicted in formula **2**, since they were obtained as intermediates or by-products in syntheses aimed specifically at clavulanic acid analogs **3** and carried out mostly by Beecham chemists[6~10]. Moreover, these compounds **2** were obtained in most cases, except for 2-ethyl derivative (**2**, R=Et, R_1=K)[11], as a form of 3-carboxylic acid ester and not as a free acid probably due to unusual instability of the latter. Some 6-substituted oxapenem esters **4** were also synthesized as a mixture of C-5 stereoisomers. Thus a mixture of methyl

† An account of this work was presented by W. N. at the 16th International Conference on Chemistry of Natural Products (IUPAC), Kyoto, May 29~June 3, 1988[1]. Details of this work were also presented by M. MURAKAMI at the 55th Symposium of Synthetic Organic Chemistry, Tokyo, June 1~2, 1989[2].



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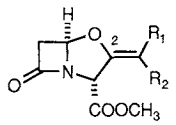

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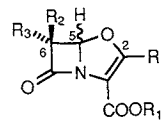
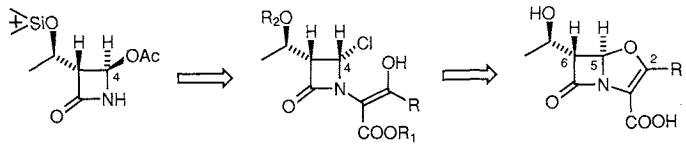


4a $R=R_1=CH_3$ $R_2=TrNH$ $R_3=H$
4b $R=CH_3$ or CH_2Cl $R_1=PNB$ $R_2=H$ $R_3=C_2H_5$

Scheme 1.



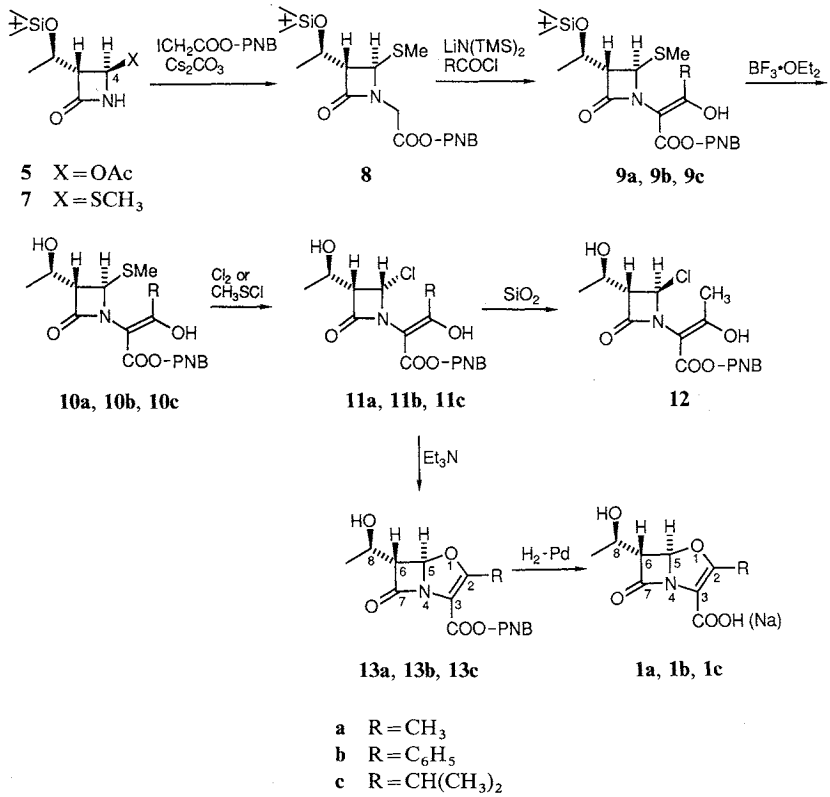
5 **6** **1**

2-methyl-6β-tritylamino-1-oxapenem-3-carboxylate and its C-5 stereoisomer **4a** was synthesized from penicillin by the Beecham chemists and the process used for this synthesis provided a prototype for the following oxapenem syntheses[12]. Some years later, 2-methyl- or 2-chloromethyl-6α-ethyl-1-oxapenem-3-carboxylic acid *p*-nitrobenzyl (PNB) ester **4b** was also synthesized by IHARA *et al.*[13] as a 1:1 mixture of the C_5-epimers by applying the aforementioned prototype synthetic route. Unfortunately, these esters could not be transformed into the corresponding free acids.

At the beginning of our work, we decided to apply the prototype route for our synthesis starting from the commercially available 3α-[1'(*R*)-*tert*-butyldimethylsilyloxy]ethyl-4β-acetoxyazetidinone (**5**) as shown in Scheme 1, whereby we expected that the 1'-(*R*)-hydroxy or its silyl-protected substituent on the C_3 ethyl side-chain (azetidinone nomenclature) could favorably control the stereochemistry at C_4 in the azetidinone (**6**) and hence at C_5 in the oxapenem compounds **1**. Our first target was 2-methyl-6α-hydroxyethyl-1-oxapenem-3-carboxylic acid **1** ($R=CH_3$) as a representative oxapenem compound.

Commercially available optically active [3(*R*),4(*R*),1'(*R*)]azetidinone **5** was treated with sodium methylthiolate to obtain in 88% yield the 4β-methylthioazetidinone **7** which was alkylated with PNB iodoacetate in acetonitrile in the presence of cesium carbonate to afford the *N*-substituted azetidinone **8** in 70% yield. This compound represents a common intermediate for the synthesis of various 2-substituted oxapenems as described below. Compound **8** was first treated with one molar equivalent of lithium hexamethyldisilazane to yield a carbanion and then treated successively with another molar equivalent of the base and one molar amount of acetyl chloride in tetrahydrofuran at $-78°C$ to obtain a single acetylated product **9a**. This compound was found to exist in an enol form as evidenced by the appearance of one proton signal at 12.3 ppm in its NMR spectrum. At this stage, removal of the *tert*-butyldimethylsilyl protecting group was necessary and this was effected by treatment with boron trifluoride etherate to give the hydroxyethyl azetidinone **10a** in 88% yield. This compound was then reacted with chlorine at $-78°C$ to afford a single chlorinated product in 71% yield. A large coupling constant of 5 Hz between C_3 and C_4 protons in its NMR spectrum clearly indicates *cis* configuration for the C_3 and C_4 substituents on the azetidinone ring. Thus, the 4α-chloro structure **11a** should be assigned to this product. The 4α-chloroazetidinone (**11a**) was found to be unstable and easily epimerized to the 4β-chloroazetidinone (**12**), when left standing in solution with facilitation by silica gel. The latter compound was thus thought

Scheme 2.



5 X=OAc
7 X=SCH_3

8

9a, 9b, 9c

10a, 10b, 10c

11a, 11b, 11c

12

13a, 13b, 13c

1a, 1b, 1c

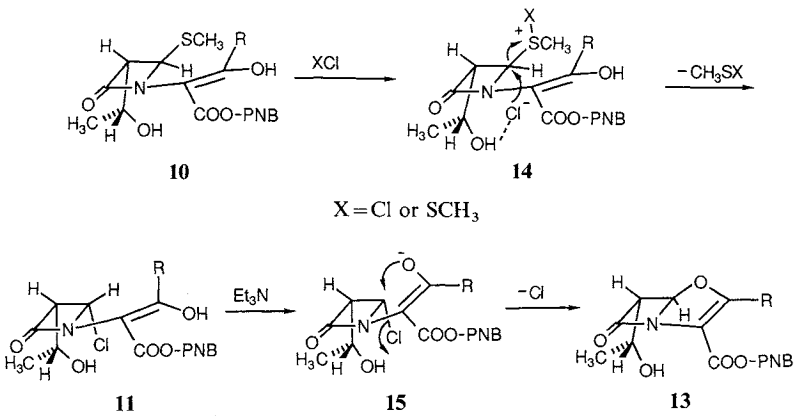
a R=CH_3
b R=C_6H_5
c R=$CH(CH_3)_2$

to be a thermodynamically more stable isomer. Next, ring closure of 4α-chloroazetidinone (**11a**) was examined and this was nicely effected by treatment with triethylamine in tetrahydrofuran at 0°C to afford the PNB oxapenem-3-carboxylate (**13a**) as crystals in 56% yield. This oxapenem ester **13a** was finally subjected to catalytic hydrogenation on palladium catalyst to afford the targeted 2-methyl-6α-hydroxyethyl-1-oxapenem-3-carboxylic acid (**1a**) as its sodium salt. The yield of this conversion was only 7% reflecting the general instability of compounds of this ring system. The stereochemical results observed through this synthesis will be discussed collectively later in this paper.

In searching for a more stable oxapenem derivative, we planned to prepare oxapenems substituted at C_2 with a variety of alkyl or aryl groups. Among them, the phenyl and isopropyl groups were chosen preferentially, since the phenyl group was reported[14] to stabilize the molecule more effectively than the methyl one in the carbapenem system and the isopropyl group was also thought to be effective due to its electron-donating property as well as its bulk which prevented attack from various kinds of reactants.

The synthesis was carried out in parallel with the synthesis of the 2-methyl analog **1a**. Thus the common intermediate **8** was acylated with 2 molar equivalents of lithium hexamethyldisilazane and one molar equivalent of benzoyl or isobutyryl chloride at −78°C to obtain, respectively in 79% or 71% yield, the benzoyl or the isobutyryl derivative **9b** or **9c** which was then desilylated smoothly with boron trifluoride etherate to the 6α hydroxyethyl derivative **10b** or **10c** in 86% or 85% yield, respectively. The NMR spectra of these compounds indicated that unlike the methyl analogs, they existed as a roughly 1 : 1 mixture of the keto and the enol forms. While the chlorination of the benzoyl derivative **10b** was effected by using

Scheme 3.



chlorine at −78°C to afford the 4α-chloroazetidinone (**11b**) in 67% yield, parallel chlorination of the isobutyryl derivative **10c** gave only a poor result. However, this conversion could be dramatically improved by changing the chlorination reagent from chlorine to methanesulfenyl chloride. Chlorination with the latter reagent at an elevated temperature (0°C) proceeded smoothly to afford the expected 4α-chloro azetidinone **11c** in excellent yield. This favorable result may be due to almost exclusive attack of this reagent at the 4β-methylthio group in **10c** without any accompanying side reactions at the β-ketoester moiety. Dimethyl disulfide produced in this chlorination, has no chlorination capability and thus may not bring about any side-reaction. Compounds **11b** and **11c** were treated with triethylamine at 0°C to effect the ring closure affording the expected oxapenem PNB esters **13b** as crystals and **13c** as an oil. While the yield of **13b** was only 19%, the yield of the isopropyl oxapenem ester **13c** was *ca.* 55%, suggesting the remarkable stability of the latter. Finally, both PNB esters underwent palladium-catalytic hydrogenation to afford the free acids **1b** and **1c** as their sodium salts in 15% and 51% yield, respectively. The marked difference in the yields reflectes the stability difference of **1b** and **1c** (*vide infra*).

As described above, the 2-substituted oxapenems bearing the hydroxyethyl side-chain at the 6α position were successfully synthesized† in the form of sodium salts suitable for biological testing. Here we emphasize that the synthesis was stereochemically well controlled. Each step producing a new chiral center, that is, the chlorination and the subsequent ring closure to the oxapenem ring, was highly stereoselective. This is in contrast with the reported synthesis[13] of the 2-substituted-6α-ethyloxapenems **4b** in which both the chlorination and the ring closure gave a mixture of two stereoisomers. Most probably, this difference is due to the structural difference between the 3α-substituents in the azetidinone intermediates. While in IHARA's synthesis the 3α-substituent is simply ethyl, in our synthesis it is the ethyl hydroxylated at the 1′-position with the (*R*) absolute configuration as depicted in formula **10** (Scheme 3), which, we assume, represents the most favorable conformation for **10**. In this conformation, the chiral 1′ carbon is located below the azetidinone ring and the methyl and the hydroxy groups on that carbon are oriented outside of the ring as shown to avoid a probable steric hindrance. Chlorination forms an intermediate sulfonium

† After our work had been finished and preliminary accounts had been presented at two scientific meetings (see the footnote on p. 1441 and refs 1 and 2), we were made aware of a similar work by PFAENDLER and HENDEL described in a Japanese patent (PFAENDLER, H. R. & H. HENDEL: Jpn. Pat. 042484 ('89)). They had also succeeded in the syntheses of 6α-hydroxyethyl-oxapenems variously alkylated at the 2 position which were carried out in a similar way to ours and reported that the 2-tertiary carbon-substituted oxapenems proved to be the most stable.

chloride **14** in which the chloride counter ion is located in the α-side of the azetidinone ring and is hydrogen-bonded† with the hydroxyl on carbon 1′. The chloride ion then attacks the C-4 carbon releasing the methanesulfenyl chloride (CH_3SCl when X is chlorine) in an SN_2 manner to form the 4α-chloroazetidinone (**11**). On treatment of this compound with triethylamine, principally an intramolecular SN_2 type replacement occurs at the C_4 carbon with the attack of the enolate from the β-side as shown in **15**, giving eventually the 5,6 *trans* oxapenem (**13**). We believe that this interpretation is reasonable and well explains the observed stereochemical course involved in the chlorination and the subsequent ring-closure processes.

Stability and Biological Properties

The half-lives of 6α-hydroxyethyl oxapenems substituted at C-2 with methyl (**1a**), phenyl (**1b**), and isopropyl (**1c**), determined in pH 7.0 buffer solution at 37 °C, were 43, 24, and 200 minutes, respectively. Unexpectedly, the stability of the 2-phenyl derivative **1b** was lower than that of the 2-methyl derivative **1a**, in disagreement with the data reported[14] for the carbapenem system. However the $t_{1/2}$ of 200 minutes for the isopropyl derivative **1c** was favorably much longer than we had expected.

The *in vitro* antibacterial activity of three oxapenems **1a**, **1b**, and **1c** was determined by the agar dilution method and the results are summarized in Table 1. As can be seen from this table, the MICs are high for all the compounds and none of them are useful. However, it is interesting to note that the antibacterial activity parallels the stability observed for the compounds, that is, the 2-isopropyl oxapenem (**1c**) with considerable stability exhibits noticeable antibacterial activity, while the unstable oxapenems **1a** and **1b** are virtually inactive.

Clavulanic acid and the carbapenem derivatives

Table 1. *In vitro* activity of 6α-hydroxyethyl-1-oxapenems (μg/ml).

	1a	**1b**	**1c**
Staphylococcus aureus FDA 209P JC-1	100	>100	6.3
S. aureus SR14	>100	>100	25
Streptococcus pyogenes C 203	100	25	1.6
S. pneumoniae Type 1	12.5	3.1	<0.8
Escherichia coli NIHJ JC-2	100	>100	25
E. coli EC-14	>100	100	6.3
Proteus mirabilis PR-4	>100	>100	25
P. vulgaris CN-329	>100	>100	50

Table 2. Inhibitory activity of β-lactamase inhibitors.

Source of β-lactamase[a]	Type[b]	Minimum effective concentration (μg/ml)[c]				
		1a	**1b**	**1c**	*epi*-Thienamycin B	Clavulanic acid
Escherichia coli SR6	C	0.002	0.032	0.016	0.016	250
Morganella morganii SR7	C	0.016	0.008	0.008	0.032	>250
Providencia stuartii SR1031	C	0.25	0.016	0.032	0.25	>250
Enterobacter cloacae SR92	C	0.008	0.032	0.016	0.016	>250
Proteus vulgaris SR31	C	0.5	8	1	4	1
Klebsiella oxytoca SR696	P	32	63	>63	>63	0.063
E. coli W3110 (RTEM)[d]	P	63	16	16	8	0.063
E. coli ML1410 (RGN 238)[d]	P	0.125	0.063	0.063	0.125	4

[a] Enzymes were crude extracts.
[b] C: Cephalosporinase; P: penicillinase.
[c] The minimum effective concentration was determined by a spot test using Nitrocefin.
[d] Plasmid-mediated β-lactamase.

† Clear-cut IR spectral evidence was given for this type of hydrogen bond in quaternary ammonium halogenides in which a hydroxy group is located near the quaternary center.[15]

are known to have strong β-lactamase inhibitory properties. As the oxapenem molecule can be regarded as a structural hybrid between clavulanic acid and a carbapenem, we were interested in knowing whether the compounds would actually exhibit inhibition against β-lactamases and if so, which type of inhibition, the clavulanic type resulting from C_5-O bond fission or the carbapenem type as anticipated from the similarity of the whole molecule including the hydroxyethyl side chain at C_6. Thus, the *in vitro* activity was determined against various penicillinases and cephalosporinases and the results are listed in Table 2 together with those for *epi*-thienamycin B and clavulanic acid as the reference compounds. Clearly, every oxapenem derivative exhibits strong inhibition against most of the cephalosporinases used and also some penicillinases indicating that the inhibition spectrum is similar to that for *epi*-thienamycin B and not that for clavulanic acid. The answer to another interesting question on the mode of inhibition, *i.e.*, whether the inhibitory action of the oxapenems is reversible or irreversible, must await further investigation of interactions between β-lactamases and these compounds.

Experimental

MP's were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained on a Hitachi 260-10 spectrophotometer and ^{1}H NMR spectra recorded on Varian EM-390 and VXR-200 spectrometers using TMS as an internal standard. UV spectra were obtained on a Hitachi 320 spectrometer. Unless otherwise stated, IR and ^{1}H NMR spectra were recorded in $CHCl_3$ and $CDCl_3$ solutions, respectively. All reactions were carried out in a nitrogen atmosphere under anhydrous conditions using solvents dried over Molecular Sieves type 4A, and all the organic solvent extracts of the reaction products were dried with anhydrous sodium sulfate.

(3*S*,4*R*)-3-[(*R*)-1-(*tert*-Butyl)dimethylsilyloxyethyl]-4-methylthioazetidin-2-one (**7**)

To a stirred solution of 4-acetoxy azetidinone **5** (8.6 g) in methanol (90 ml) was added a mixture of 1 N aq NaOH (36 ml) and a 30% methanol solution of MeSH (8.4 ml). After being stirred for 45 minutes at room temperature, the reaction mixture was concentrated under reduced pressure and extracted with EtOAc. The EtOAc solution was washed with brine, dried, and evaporated under reduced pressure, leaving an oily residue. Purification of the residue by column chromatography on silica gel gave **7** (7.29 g, 88%) as a colorless solid: ^{1}H NMR δ 0.82 (9H, s, *tert*-Bu), 1.16 (3H, d, J=6.0 Hz, CH_3CHOSi), 2.07 (3H, s, SMe), 3.04 (1H, m, 3-H), 4.16 (1H, m, CH_3C*H*OSi), 4.68 (1H, d, J=2.0 Hz, 4-H), 6.83 (1H, br s, NH).

PNB (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyl)dimethylsilyloxyethyl]-4-methylthio-2-oxo-1-azetidineacetate (**8**)

To a stirred solution of **7** (4.3 g) in CH_3CN (40 ml) was added PNB iodoacetate (6.01 g) and $CsCO_3$ (6.09 g). After being stirred for 16 hours at room temperature, the reaction mixture was poured into cold dil HCl and extracted with EtOAc. The organic layer was washed with a cold $NaHCO_3$ solution and brine, dried, and evaporated. The residue, purified by column chromatography on silica gel, gave **8** (5.10 g, 70%): ^{1}H NMR δ 0.85 (9H, s, *tert*-Bu), 1.26 (3H, d, J=6.0 Hz, CH_3CHOSi), 2.05 (3H, s, SMe), 3.19 (1H, m, 3-H), 3.86 and 4.17 (2H, ABq, J=17.6 Hz, NCH_2COO), 4.86 (1H, d, J=2.0 Hz, 4-H), 5.24 (2H, s, CH_2Ar), 7.51 (2H, d, J=9.0 Hz, Ar-H), 8.23 (2H, d, J=9.0 Hz, Ar-H).

PNB (3*S*,4*R*)-α-Acetyl-3-[(1*R*)-1-(*tert*-butyl)dimethylsilyloxyethyl]-4-methylthio-2-oxo-1-azetidineacetate (**9a**)

To a cold solution of **8** (2.06 g) in THF (16 ml) was added a 1 M THF solution of $LiN(SiMe_3)_2$ (4.7 ml) at −78°C and the mixture was kept at −78°C for 15 minutes under stirring. To this mixture were added the 1 M THF solution of $LiN(SiMe_3)_2$ (4.3 ml) and acetyl chloride (0.34 ml). After being stirred for 30 minutes at about −78°C, the reaction mixture was poured into cold dil HCl, and extracted with EtOAc. The organic layer was washed with a cold $NaHCO_3$ solution and brine, dried, and evaporated. The residue, purified by column chromatography on silica gel, gave **9a** (1.59 g, 71%): IR (cm^{-1}) 1756, 1655, 1602, 1519,

1420, 1375, 1344; ^{1}H NMR δ 0.82 (9H, s, *tert*-Bu), 1.21 (3H, d, J=6.0 Hz, C*H*$_3$CHOSi), 1.99 (3H, s, SMe), 2.10 (3H, s, C=CC*H*$_3$), 3.10 (1H, m, 3-H), 4.17 (1H, m, CH$_3$C*H*OSi), 4.87 (1H, d, J=2.0 Hz, 4-H), 5.19 and 5.38 (2H, ABq, J=13.5 Hz, C*H*$_2$Ar), 7.51 (2H, d, J=9.0 Hz, Ar-H), 8.18 (2H, d, J=9.0 Hz, Ar-H), 12.27 (1H, s, C=CHO*H*).

PNB (3*S*,4*R*)-α-Acetyl-3-[(1*R*)-1-hydroxyethyl]-4-methylthio-2-oxo-1-azetidineacetate (**10a**)

To a cold solution of **9a** (2.37 g) in CH_3CN (20 ml) was added $BF_3 \cdot OEt_2$ (0.96 ml) at −25°C. After being stirred for 30 minutes at around this temperature, the reaction mixture was poured into a cold $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated. The residue, purified by column chromatography on silica gel, gave **10a** (1.59 g, 71%): IR (cm^{-1}) 3300, 1745, 1653, 1602, 1514, 1412, 1373, 1340; ^{1}H NMR δ1.31 (3H, d, J=6.3 Hz, C*H*$_3$CHOH), 2.10 (3H, s, SMe), 2.17 (3H, s, C=CC*H*$_3$), 3.17 (1H, m, 3-H), 4.25 (1H, m, CH$_3$C*H*OH), 4.95 (1H, d, J=3.0 Hz, 4-H), 5.33 (2H, s, CH$_2$Ar), 7.20 (1H, s, OH), 7.57 (2H, d, J=9.0 Hz, Ar-H), 8.23 (2H, d, J=9.0 Hz, Ar-H), 12.29 (1H, s, C=CHO*H*).

PNB (3*S*,4*S*)-α-Acetyl-4-chloro-3-[(1*R*)-1-hydroxyethyl]-2-oxo-1-azetidineacetate (**11a**)

To a cold solution of **10a** (800 mg) in CH_2Cl_2 (14 ml) was added dropwise a 1 M CCl_4 solution of Cl_2 (2.02 ml) at −78°C. After being stirred for 10 minutes at the same temperature, the reaction mixture was poured into a cold aqueous sodium thiosulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated. The residue was purified by column chromatography on silica gel, giving **11a** (550 mg, 71%): IR (cm^{-1}) 3515, 3320, 1768, 1658, 1604, 1518, 1420, 1374, 1340; ^{1}H NMR δ 1.46 (3H, d, J=6.0 Hz, C*H*$_3$CHOH), 2.16 (3H, s, C=CC*H*$_3$), 2.18 (1H, s, OH), 3.51 (1H, m, 3-H), 4.36 (1H, m, CH$_3$C*H*OH), 5.33 (2H, s, CH$_2$Ar), 5.88 (1H, d, J=5.0 Hz, 4-H), 7.51 (2H, d, J=9.0 Hz, Ar-H), 8.23 (2H, d, J=9.0 Hz, Ar-H), 12.26 (1H, s, C=CHO*H*).

PNB (5*R*,6*R*)-6α-[(1*R*)-1-Hydroxyethyl]-2-methyl-1-oxa-2-penem-3-carboxylate (**13a**)

To a cold solution of **11a** (550 mg) in THF (20 ml) was added Et_3N (0.21 ml) at 0°C. After being stirred for 10 minutes at 0°C, the reaction mixture was poured into cold dil HCl and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated. The residue was solidified from ether, giving **13a** (280 mg, 56%); mp 123~125°C; liquid secondary (LSI-MS m/z 349 $(M+H)^+$, 697 $(2M+H^+)$; IR (cm^{-1}) 3575, 3380, 1796, 1705, 1628, 1602, 1515, 1380, 1348; ^{1}H NMR δ1.38 (3H, d, J=7.0 Hz, C*H*$_3$CHOH), 2.29 (3H, s, 2-CH$_3$), 3.66 (1H, d, J=5.0 Hz, 6-H), 4.27 (1H, m, CH$_3$C*H*OH), 5.23 and 5.45 (2H, ABq, J=13.1 Hz, CH$_2$Ar), 5.91 (1H, s, 5-H), 7.61 (2H, d, J=9.0 Hz, Ar-H), 8.22 (2H, d, J=9.0 Hz, Ar-H).

Sodium (5*R*,6*R*)-6α-[(1*R*)-1-Hydroxyethyl]-2-methyl-1-oxa-2-penem-3-carboxylate (**1a**)

A solution of the PNB ester **13a** (350 mg) in EtOAc (22 ml) was mixed with 10% Pd-C (600 mg) and catalytically hydrogenated under stirring for 5 hours at room temperature. The catalyst was filtered and the filtrate was washed with a 0.1 M phosphate buffer solution (pH 7). The aqueous layer was chromatographed on Diaion HP-20 (non-ionic adsorption resin). Lyophilization of the product fractions gave **1a** (20 mg, 7%). The purity of **1a** was 92% as determined by the HPLC area percentage method. UV $\lambda_{max}^{H_2O}$ nm 260; ^{1}H NMR (D_2O) δ 1.87 (3H, d, J=6.0 Hz, C*H*$_3$CHOH), 2.75 (3H, s, 2-CH$_3$), 4.36 (1H, d, J=5.0 Hz, 6-H), 4.74 (1H, m, CH$_3$C*H*OH), 6.42 (1H, s, 5-H).

PNB (3*S*,4*R*)-α-Benzoyl-3-[(*1R*)-1-(*tert*-butyl)dimethylsilyloxyethyl]-4-methylthio-2-oxo-1-azetidineacetate (**9b**)

9b was prepared from **8** in 79% yield as described for **9a**. IR (cm^{-1}) 1756, 1688, 1600, 1520, 1446, 1345; ^{1}H NMR δ 0.86 (9H, s, *tert*-Bu), 1.1~1.4 (3H, m, C*H*$_3$CHOSi), 1.83 (3H, s, SMe), 3.05 (1H, m, 3-H), 4.25 (1H, m, CH$_3$C*H*OSi), 5.3~5.5 (3H, m, 4-H, CH$_2$Ar), 6.11 (1H, s, C*H*COPh), 7.5~8.3 (4H, m, Ar-H) 12.70 (1H, s, C=CO*H*).

PNB (3*S*,4*R*)-α-Benzoyl-3-[(1*R*)-1-hydroxyethyl]-4-methylthio-2-oxo-1-azetidineacetate (**10b**)

10b was prepared from **9b** in 86% yield as described for **10a**. ^{1}H NMR δ 1.26 (3H, m, C*H*$_3$CHOH),

1.80 (3H, s, SMe), 3.16 (1H, m, 3-H), 4.20 (1H, m, CH_3CHOSi), 5.32 (1H, d, J=2.0 Hz, 4-H), 5.39 (2H, s, CH_2Ar), 6.07 (1H, s, CH-COPh), 7.4~8.3 (9H, m, Ar-H), 12.74 (1H, s, C=COH).

PNB (3*S*,4*S*)-α-Benzoyl-4-chloro-3-[(1*R*)-1-hydroxyethyl]-2-oxo-1-azetidineacetate (**11b**)

11b was prepared from **10b** in 67% yield as described for **11a**. IR (cm^{-1}) 3350, 1780, 1693, 1655, 1606, 1518, 1350; ^1H NMR δ 1.37 (3H, m, CH_3CHOH), 3.50 (1H, m, 3-H), 4.23 (1H, m, CH_3CHOH), 5.30 (1H, d, J=5.0 Hz, 4-H), 5.40 (2H, s, CH_2Ar), 6.15 (1H, m, CHCOPh), 7.4~8.4 (9H, m, Ar-H), 12.72 (1H, s, C=COH).

PNB (5*R*,6*R*)-6α-[(1*R*)-1-Hydroxyethyl]-2-phenyl-1-oxa-2-penem-3-carboxylate (**13b**)

13b was prepared from **11b** in 19% yield as described for **13a**. MP 128~129°C; LSI-MS m/z 411 $(M+H)^+$, 821 $(2M+H^+)$; IR (cm^{-1}) 3300, 1793, 1698, 1600, 1515, 1342, 1310; ^1H NMR δ 1.42 (3H, d, J=6.0 Hz, CH_3CHOH), 3.78 (1H, d, J=5.0 Hz, 6-H), 4.35 (1H, m, CH_3CHOH), 5.26 and 5.44 (2H, ABq, J=10.4 Hz, CH_2Ar), 6.07 (1H, s, 5-H), 7.3~8.5 (9H, m, Ar-H).

Sodium (5*R*,6*R*)-6α-[(1*R*)-1-Hydroxyethyl]-2-phenyl-1-oxa-2-penem-3-carboxylate (**1b**)

1b was prepared from **13b** in 15% yield as described for **1a**. The purity of **1b** was 72% as determined by the HPLC area percentage method. UV $\lambda_{max}^{H_2O}$ nm 294; IR (KBr) cm^{-1} 3360, 1771, 1670, 1583, 1486, 1440, 1380; ^1H NMR (D_2O) δ 1.83 (3H, d, J=6.0 Hz, CH_3CHOH), 4.40 (1H, d, J=6.0 Hz, 6-H), 4.77 (1H, m, CH_3CHOH), 6.49 (1H, s, 5-H), 7.9~8.3 (5H, m, Ar-H).

PNB (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyl)dimethylsilyloxyethyl]-α-isobutyryl-4-methylthio-2-oxo-1-azetidineacetate (**9c**)

9c was prepared from **8** in 71% yield as described for **9a**. IR (cm^{-1}) 1756, 1653, 1601, 1518, 1350; ^1H NMR δ 0.85 (9H, s, *tert*-Bu), 1.1~1.3 (9H, m, CH_3CHOSi, $CH(CH_3)_2$), 2.04 (3H, s, SMe), 2.9~3.2 (2H, m, 3-H, $CHMe_2$), 4.30 (1H, m, CH_3CHOSi), 4.82 (1H, d, J=2.0 Hz, 4-H), 5.29 (2H, s, CH_2Ar), 7.56 (2H, d, J=9.0 Hz, Ar-H), 8.25 (2H, d, J=9.0 Hz, Ar-H), 12.47 (1H, brs, C=COH).

PNB (3*S*,4*R*)-3-[(1*R*)-1-Hydroxyethyl]-α-isobutyryl-4-methylthio-2-oxo-1-azetidineacetate (**10c**)

10c was prepared from **9c** in 85% yield as described for **10a**. IR (cm^{-1}) 3350, 1755, 1658, 1603, 1520, 1252; ^1H NMR δ 1.1~1.4 (9H, m, CH_3CHOH, $CH(CH_3)_2$), 2.10 (3H, s, SMe), 2.8~3.2 (2H, m, 3-H, $CHMe_2$), 4.20 (1H, m, CH_3CHOH), 4.93 (1H, brs, 4-H), 5.31 (2H, s, CH_2-Ar), 7.56 (2H, d, J=9.0 Hz, Ar-H), 8.20 (2H, d, J=9.0 Hz, Ar-H).

PNB (3*S*,4*S*)-4-Chloro-3-[(1*R*)-1-hydroxyethyl]-α-isobutyryl-2-oxo-1-azetidineacetate (**11c**)

To a cold solution of **10c** (115 mg) in CH_2Cl_2 (3 ml) was added 1 M CCl_4 solution of MeSCl (0.5 ml) at 0°C and the stirring was continued for 30 minutes at this temperature. Then, a cold mixture of CH_2Cl_2 (10 ml), EtOAc (10 ml) and silica gel (3 g) was added. After being stirred for 5 minutes with keeping the temperature at 0°C, the mixture was filtered and the filtrate was evaporated under reduced pressure with maintaining the temperature below 15°C, giving an oily **11c** (110 mg). IR (cm^{-1}) 3350, 1768, 1648, 1597, 1514, 1342; ^1H NMR δ 1.1~1.5 (9H, m, $CH(CH_3)_2$, CH_3CHOH), 2.93 (1H, m, $CHMe_2$), 3.47 (1H, m, 3-H), 4.36 (1H, m, CH_3CHOH), 5.30 (2H, s, CH_2Ar), 5.79 (1H, d, J=4.5 Hz, 4-H), 7.47 (2H, d, J=9.0 Hz, Ar-H), 8.23 (2H, d, J=9.0 Hz, Ar-H), 12.41 (1H, s, C=COH).

PNB (5*R*,6*R*)-6α-[(1*R*)-1-Hydroxyethyl]-2-isopropyl-1-oxa-2-penem-3-carboxylate (**13c**)

13c was prepared from **11c** in *ca.* 55% yield as an oil as described for **13a**. IR cm^{-1} 3460, 1795, 1719, 1612, 1517, 1460, 1442, 1375, 1342; ^1H NMR δ 1.1~1.5 (9H, m, $CH(CH_3)_2$, CH_3CHOH), 3.57 (1H, m, 6-H), 4.23 (1H, m, CH_3CHOH), 5.21 and 5.44 (2H, ABq, J=29.0 Hz, CH_2Ar), 6.89 (1H, s, 5-H), 7.60 (2H, d, J=9.0 Hz, Ar-H), 8.23 (2H, d, J=9.0 Hz, Ar-H).

Sodium (5*R*,6*R*)-6α-[(1*R*)-1-Hydroxyethyl]-2-isopropyl-1-oxa-2-penem-3-carboxylate (**1c**)

1c was prepared from **13c** in 51% yield as described for **1a**. The purity of **1c** was 71% as determined by the HPLC area percentage method. UV $\lambda_{max}^{H_2O}$ nm 263; IR (KBr) cm^{-1} 3400, 1774, 1634, 1572, 1403; ^1H

NMR (D_2O) δ 1.5~1.9 (9H, m, CH_3CHOH, $CH(CH_3)_2$), 4.26 (1H, d, J=6.0 Hz, 6-H), 4.67 (1H, m, CH_3CHOH), 6.33 (1H, s, 5-H).

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