STRUCTURES OF OA-6129D AND E, NEW CARBAPENAM ANTIBIOTICS

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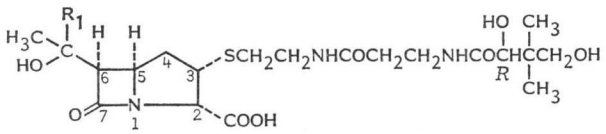
The structures and stereochemistry of OA-6129D and E, new carbapenam compounds produced by *Streptomyces* sp. OA-6129, were determined by spectroscopic analysis and chemical transformation.

In previous papers, we have reported the fermentation, isolation[1], structures[2] and antimicrobial activities[3] of OA-6129A, B_1, B_2 and C, new carbapenem antibiotics having a pantetheinyl side chain at C-3*. These antibiotics were converted to PS-5, epithienamycins A and C and MM 17880, respectively, in the presence of acetyl CoA by action of an acylase, showing that the OA-6129 group of compounds were key intermediates in the biosynthesis of carbapenems[4]. In our working hypothesis of carbapenem biosynthesis, a carbapenam compound having the C-3 pantetheinyl side chain was expected to exist as a precursor for No. 17927D (3-(2-acetamidoethyl)thio-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid)[5,6] in *Streptomyces* sp. OA-6129. In this paper we describe the isolation and structure determination of OA-6129D (**1**) and E (**2**), new carbapenam compounds having the pantetheinyl side chain at C-3.

Fermentation, Isolation and Physico-chemical Properties

One hundred milliliters each of seed medium S-1 (soybean meal 15, yeast extract 5, potato starch 20, $CaCO_3$ 2 g/liter, pH 7.0) was distributed in a 500-ml Erlenmeyer flask and was sterilized at 120°C for 15 minutes. A loopful each of mature spores of *Streptomyces* sp. OA-6129 (FERM-BP 11) was inoculated in the flask, and cultivated at 28°C for 48 hours on a rotary shaker (200 rpm, throw 7 cm). One liter of the seed culture was transferred to a 1,000-liter fermentor containing 600 liters of production medium GM-1 (glycerol 80, fish meal 10, soybean meal 30, $CaCO_3$ 3, K_2HPO_4 2, $MgSO_4$ 2, vitamin B_{12} 0.005 g/liter, pH 7.2) and cultivated at 28°C for 70 hours (20 hours shorter than the usual fermentation period for OA-6129A, B and C) at an aeration rate of 500 liters/minute and an agitation rate of 150 rpm. As an antifoamer, 0.07% of Silicone KM-75 was added.

Fig. 1.



OA-6129D (**1**) R_1=H
OA-6129E (**2**) R_1=CH_3

* The numbering system employed in this paper is shown in Fig. 1.

By column chromatography[1] with Diaion HP-20, Diaion PA-306S, Bio-Gel P-2, QAE-Sephadex A-25 and Sephadex G-10 (Fig. 2), OA-6129C, B and A were removed. The remaining antimicrobially active fraction composed of the sodium salts of antibiotics OA-6129B_2, D and E was esterified at room temperature for 3 hours with *p*-nitrobenzyl bromide in dimethylformamide containing triethylamine. The reaction mixture was column-chromatographed on silica gel, giving OA-6129D *p*-nitrobenzyl ester (*p*NB) (**3**) (Rf 0.52) and OA-6129E·*p*NB (**4**) (Rf 0.55) on a silica gel thin-layer chromatographic (TLC) plate developed with a 1 : 3 mixture of benzene - acetone. Both carbapenam esters exhibited extremely weak antimicrobial activity against *Comamonas terrigena* in a disc-agar diffusion assay plate containing horse serum. **3** and **4** were separately acetonated at room temperature for 30 minutes with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid in acetone. Silica gel

Fig. 2.

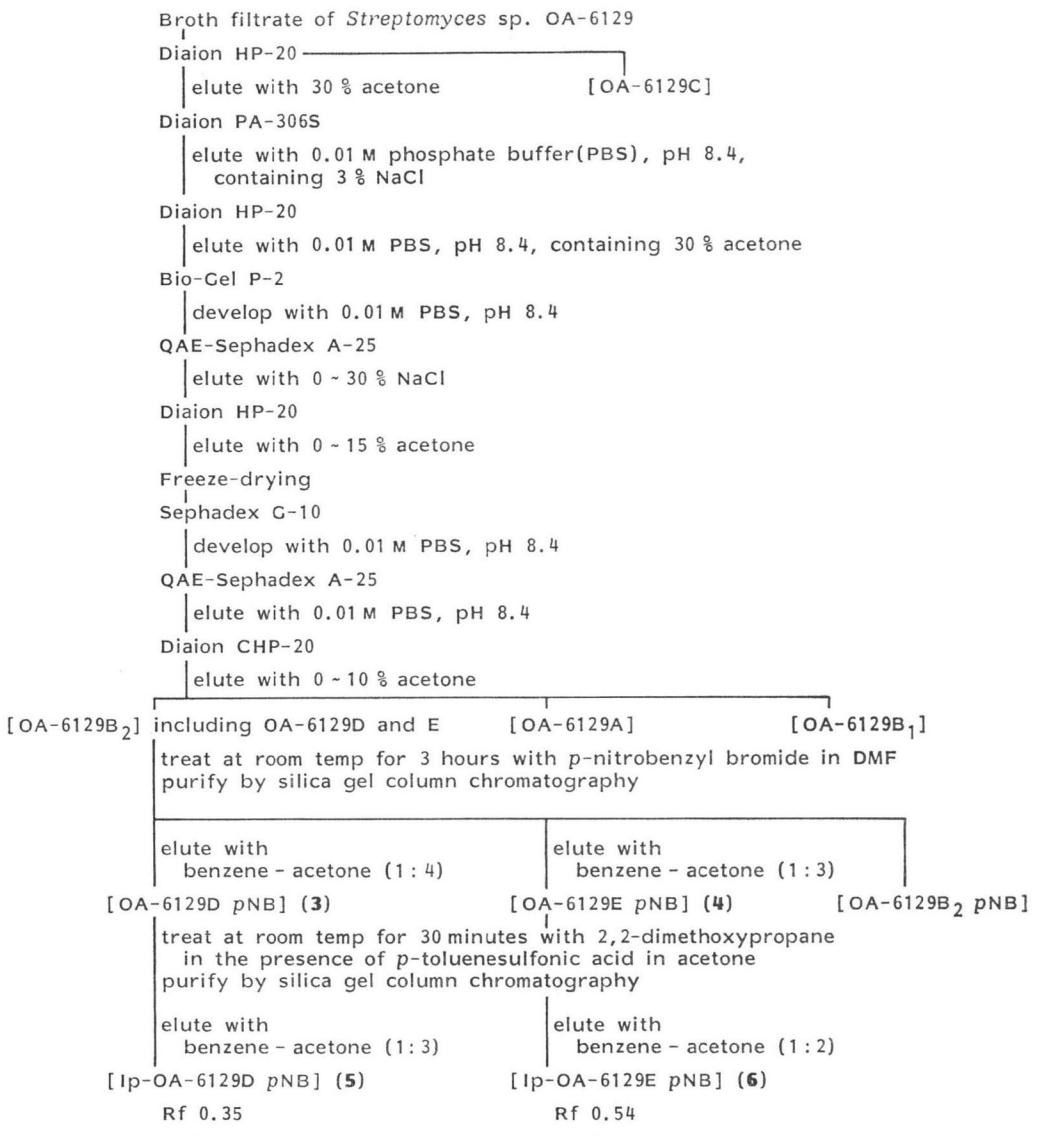


Table 1. Physico-chemical properties of Ip-OA-6129D·*p*NB (**5**) and Ip-OA-6129E·*p*NB (**6**).

	5	**6**
$[\alpha]_D^{24}$	+20.3° (*c* 1.0, CH_2Cl_2)	+12.6° (*c* 1.0, $CHCl_3$)
IR $\nu_{max}^{CHCl_3}$ cm^{-1}	3400, 2975, 1750, 1660, 1515, 1345, 1170, 1090	3400, 2975, 1750, 1660, 1515, 1345, 1180, 1090
UV $\lambda_{max}^{CH_2Cl_2}$ nm (ε)	268 (7,500)	268 (11,500)
^1H NMR ($CDCl_3$) δ	0.96 (3H, s), 1.02 (3H, s), 1.36 (3H, s), 1.42 (3H, s), 1.46 (3H, s), 1.60~2.20 (2H, m), 2.42 (2H, t, *J*=6.5 Hz), 2.50~2.70 (2H, m), 2.85 (1H, d, *J*=5.0 Hz), 3.15~3.85 (8H, m), 4.04 (1H, s), 3.90~4.20 (2H, m), 4.77 (1H, d, *J*=7.5 Hz), 5.27 (2H, s), 6.42 (1H, br), 6.97 (1H, br), 7.50 (2H, d, *J*=8.5 Hz), 8.18 (2H, d, *J*=8.5 Hz)	0.97 (3H, s), 1.03 (3H, s), 1.28 (3H, s), 1.41 (3H, s), 1.45 (3H, s), 1.46 (3H, s), 1.65~2.15 (2H, m), 2.25~2.70 (5H, m), 2.80~3.85 (8H, m), 3.90~4.30 (1H, m), 4.73 (1H, d, *J*=7.5 Hz), 5.23 (2H, s), 6.30 (1H, br), 6.93 (1H, br), 7.50 (2H, d, *J*=8.5 Hz), 8.17 (2H, d, *J*=8.5 Hz)
FD-MS (*m/z*)	651 (M+1)	664 (M)

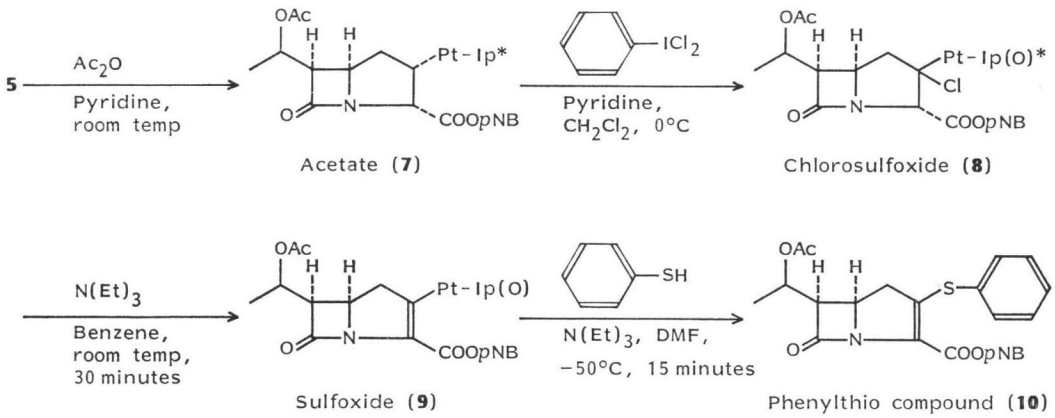
column chromatography provided isopropylidene (Ip)-OA-6129D·*p*NB (**5**) (Rf 0.35, silica gel TLC, benzene - acetone, 1 : 1) and Ip-OA-6129E·*p*NB (**6**) (Rf 0.54). The physico-chemical properties of these carbapenam derivatives are summarized in Table 1.

Structures and Stereochemistry

The IR spectrum of Ip-OA-6129D·*p*NB (**5**) showed absorption bands at 1750 (β-lactam and ester) and 1660 cm^{-1} (amide). **5** had only one UV absorption maximum at 268 nm attributable to the *p*-nitrobenzyl group, indicating that **1** possessed no characteristic UV absorption maximum. FD-MS spectrometry gave a protonated molecular ion peak of *m/z* 651 for **5** which corresponded to dihydro-Ip-OA-6129B·*p*NB[2]. This was supported by NMR spectroscopic analysis as follows: The existence of a pantotheinyl group in **1** was evidenced by two vicinal singlet dimethyls (δ 0.96 and 1.02), a triplet methylene (δ 2.42) and a singlet methine (δ 4.04). The signals of a doublet methyl (δ 1.36) and a multiplet methine (δ 3.90~4.20) were attributed to 1-hydroxyethyl at C-6. A characteristic doublet methine appearing at δ 4.77 was assigned to the proton at C-2, which turned into a singlet by irradiation of the H-3 signal at δ 3.74. Furthermore, the methylene at C-4 and the one adjacent to the sulfur atom of cysteamine were located in about 0.3 and 1.4 ppm higher fields than the corresponding signals of Ip-OA-6129B_2·*p*NB[2], respectively. These findings allowed us to assume that **1** was a carbapenam compound having a pantetheinyl group at C-3 and a 1-hydroxyethyl group at C-6.

In order to confirm this structure and further to determine the relative configuration of the two protons on the β-lactam ring, we converted the acetate **7** to the carbapenem derivatives by the methods of the Beecham[7] and our[8] groups (Fig. 3). **7** was obtained by acetylation of **5** with acetic anhydride in pyridine at room temperature. In the IR spectrum of **7**, the absorption band assigned to β-lactam carbonyl (1770 cm^{-1}) was clearly distinguished from that of ester (1740 cm^{-1}), implying that the hydrogen bonding formed in **5** between the hydroxyl group of C-6 hydroxyethyl and the carbonyl group of β-lactam. Treatment of **7** with two equivalents of iodobenzene dichloride[7] in methylene chloride containing pyridine yielded the corresponding chlorosulfoxide **8**. Elimination of hydrochloride from **8** with triethylamine resulted in a sulfoxide **9** having the carbapenem skeleton. The *S*-oxide **9** was then led to a phenylthio compound **10** by replacement with thiophenol[8]. The coupling constant in **10** between H-5

Fig. 3.



* Pt-Ip=Isopropylidenepantetheinyl.
Pt-Ip(O)=*S*-Oxide of the isopropylidenepantetheinyl group.

and H-6 was found to be 6.0 Hz, revealing that the relative configuration of the two protons on the β-lactam ring was *cis*. Thus **1** was determined to be (5,6-*cis*)-6-(1-hydroxyethyl)-7-oxo-3-pantetheinyl-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

The absolute configurations of C-2 and C-3 were deduced to be *S*, based on the findings that no epimerization occurred at C-2 by treatment of **5** with 1,5-diazabicyclo[5.4.0]undec-5-ene in methylene chloride; and that the chemical shift (δ 4.77) and the coupling constant (J=7.5 Hz) of H-2 in the NMR spectrum of **5** corresponded to 2,3-*threo*-dihydro-PS-5·*p*NB[9] among the 2-acetamidoethanethiol adducts reported by the Beecham group. Accordingly, except for the absolute configuration of 1-hydroxyethyl, **1** was concluded to be (2*S*,3*S*,5*R*,6*R*)-6-(1-hydroxyethyl)-7-oxo-3-[(*R*)-pantetheinyl]-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid.

The IR and UV spectra of Ip-OA-6129E·*p*NB (**6**) were almost identical with those of **5**. The molecular weight of **6** was determined to be 664 by FD-MS spectrometry. Excluding two new signals of singlet methyls appearing in **6** at δ 1.28 and δ 1.41 ~ 1.46 overlapping with methyls of the isopropylidene group which were assigned to a hydroxyisopropyl group, the NMR signals of **6** and **5** were indistinguishable. The *cis* configuration at H-5 and H-6 was determined from the coupling constant of H-5 ($J_{5,6}$= 6.0 Hz) at δ 4.06 by decoupling the center of C-4 methylene (δ 1.90). The structure of **2** was thus concluded to be (2*S*,3*S*,5*R*,6*R*)-6-(1-hydroxy-1-methyl)ethyl-7-oxo-3-[(*R*)-pantetheinyl]-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid.

Experimental

NMR spectra were obtained with a Varian EM 390 spectrometer with tetramethylsilane as an internal standard (δ 0 ppm). Infrared and ultraviolet spectra were recorded in a Hitachi 260-30 spectrometer and a Hitach 200-20 spectrometer respectively. Optical rotations were measured with a Jasco DIP-181 polarimeter. Field desorption mass spectra were obtained with a Hitachi RMU-7 mass spectrometer. Precoated silica gel plates F_{254} and silica gel 60 (70 ~ 230 mesh) (E. Merck, Darmstadt) were employed for thin-layer and column chromatographies respectively.

Isolation of OA-6129D *p*-Nitrobenzyl Ester (**3**) and E *p*-Nitrobenzyl Ester (**4**)

Nine hundred and sixty-eight milligrams of a pale yellow powder containing the sodium salts of

OA-6129B_2, D and E which were isolated from 600 liters of 70 hour-old fermentation broth o f*Streptomyces* sp. OA-6129[1] was dissolved in 50 ml of dimethylformamide, and then mixed with 3.6 ml of triethylamine under cooling with ice. With stirring, a solution of 4.9 g of *p*-nitrobenzyl bromide in 45 ml of dimethylformamide was added and stirred at room temperature for 3 hours. The reaction mixture was poured into 300 ml of methylene chloride, and washed with two 50 ml portions of 0.1 M phosphate buffer, pH 6.8, saturated with sodium chloride. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was dissolved in 20 ml of methylene chloride and adsorbed onto a column of 80 g of silica gel with a 1: 1 mixture of benzene - acetone. The column was successively developed with 200 ml of benzene - acetone (1: 1), 160 ml of benzene - acetone (1: 3), 160 ml of benzene - acetone (1: 4), and 320 ml of acetone. The eluate with the 1: 3 benzene - acetone mixture was concentrated to dryness to give 40 mg of a crude powder of OA-6129E *p*-nitrobenzyl ester (**4**) which showed a UV-absorbing spot at Rf 0.55 on a silica gel TLC plate developed in a 1: 4 mixture of benzene - acetone. The eluate collected with the 1: 4 mixture of benzene - acetone yielded 190 mg of OA-6129D *p*-nitrobenzyl ester (**3**), (Rf 0.52).

3: $[\alpha]_D^{24}$ +11.7° (*c* 1.0, CH_2Cl_2): IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1750 (β-lactam, ester), 1660 (amide): UV $\lambda_{max}^{CH_2Cl_2}$ nm (ε) 268 (5,500): NMR ($CDCl_3$) δ 0.90 (3H, s), 0.98 (3H, s), 1.34 (2H, d, J=6.5 Hz), 1.75~2.20 (3H, m), 2.30~2.80 (5H, m), 3.15~4.50 (12H, m), 4.77 (1H, d, J=7.0 Hz), 5.23 (2H, s), 6.70 (1H, br), 7.30~7.60 (3H, m), 8.17 (2H, d, J=8.0 Hz): FD-MS (*m/z*) 611 (M+1).

Further elution of the silica gel column with acetone provided 220 mg of OA-6129B_2 *p*-nitrobenzyl ester (Rf 0.23).

Acetonation of OA-6129D *p*-Nitrobenzyl Ester (**3**)

A solution of 52 mg of **3** in a mixture of 4 ml acetone, 0.5 ml 2,2-dimethoxypropane and 200 mg anhydrous sodium sulfate was mixed with 1.5 mg of *p*-toluenesulfonic acid. After stirring for 30 minutes, 20 μl of triethylamine was poured into the reaction mixture and the solution was concentrated to 0.5 ml under reduced pressure. Methylene chloride (80 ml) was added to the concentrate and the organic layer was recovered. After washing with 20 ml each of 0.1 M phosphate buffers, pH 8.4 and pH 6.8, the solution was dried with anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The residue was dissolved in 3 ml of methylene chloride and applied onto a silica gel (5 g) column with a 10: 1 mixture of benzene - acetone. The column was developed with mixtures of benzene and acetone (10: 1, 5: 1, 3: 1, 1: 1 and 1: 3). Fractions which showed a UV-absorbing spot at Rf 0.35 on a silica gel TLC plate (benzene - acetone, 1: 1) were combined and concentrated *in vacuo* to dryness to give 31 mg of isopropylidene-OA-6129D *p*-nitrobenzyl ester (**5**). The physico-chemical properties of **5** are presented in Table 1.

Acetonation of OA-6129E *p*-Nitrobenzyl Ester (**4**)

The crude powder of **4** (40 mg) was dissolved in a mixture of 4 ml acetone and 0.3 ml 2,2-dimethoxypropane containing 100 mg anhydrous sodium sulfate. *p*-Toluenesulfonic acid (2.5 mg) was added and stirred at room temperature for 30 minutes. After the reaction was stopped by addition of 40 μl of triethylamine, the mixture was concentrated to 0.5 ml *in vacuo*, and diluted with 100 ml of methylene chloride. The organic layer was rinsed successively with 20 ml each of 0.1 M phosphate buffers, pH 8.4 and pH 6.8, and then dried over anhydrous sodium sulfate. The evaporation residue in 4 ml of methylene chloride was applied onto a silica gel (5 g) column by using a 10: 1 mixture of benzene - acetone. The developing solvents were 10: 1, 5: 1, 3: 1, 1: 1 and 1: 2 mixtures of benzene - acetone. The fractions collected with the 1: 1 and 1: 2 mixtures of benzene - acetone were combined and concentrated *in vacuo* to give 19 mg of isopropylidene-OA-6129E *p*-nitrobenzyl ester (**6**) (Rf 0.54; SiO_2 TLC: benzene - acetone, 1: 1). The physico-chemical properties of **6** are included in Table 1.

Acetylation of **5**

5 (25 mg) in 1 ml of pyridine was acetylated with 0.32 ml of acetic anhydride at room temperature for 3 hours under stirring. The reaction mixture was diluted with 10 g of ice water, and poured into 50 ml of methylene chloride. The solution was washed with 20 ml of 0.1 M phosphate buffer pH 6.8. The organic layer was separated, dried with anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. The residue in 2 ml of methylene chloride was adsorbed onto a silica gel (5 g) column with ben-

zene. Each 20 ml of benzene - acetone mixtures (10: 0, 10: 1, 5: 1, 3: 1, 2: 1, 1: 1 and 1: 5) was employed for column elution. The eluate with the 1: 1 mixture of benzene - acetone was collected and concentrated to dryness to give 18 mg of 6-(1-acetoxyethyl)-3-isopropylidenepantetheinyl-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylic acid *p*-nitrobenzyl ester (**7**), (Rf 0.61 on a silica gel TLC plate; benzene - acetone, 1: 1).

7: $[\alpha]_D^{24}$ +12.5° (*c* 1.0, CH_2Cl_2): IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1768 (β-lactam), 1740 (ester), 1665 (amide): UV $\lambda_{max}^{CH_2Cl_2}$ nm (ε) 268 (10,100): NMR ($CDCl_3$) δ 0.97 (3H, s), 1.02 (3H, s), 1.30 (3H, d, J=6.5 Hz), 1.40 (3H, s), 1.44 (3H, s), 2.05 (3H, s), 1.80~2.28 (2H, m), 2.40 (2H, t, J=6.5 Hz), 2.55~2.90 (2H, m), 3.10~3.80 (8H, m), 4.01 (1H, s), 4.00~4.20 (1H, m), 4.72 (1H, d, J=7.0 Hz), 4.98~5.30 (1H, m), 5.23 (2H, s), 6.34 (1H, br), 6.93 (1H, br), 7.48 (2H, d, J=9.0 Hz), 8.17 (2H, d, J=9.0 Hz): FD-MS (*m/z*) 693 (M+1).

Oxidation of **7** with Iodobenzene Dichloride

A solution of 31 mg of **7** in a mixture of 1 ml of benzene and 1 ml of methylene chloride was mixed at 0°C with 16 μl of pyridine and then with 1 ml of methylene chloride containing 24 mg of iodobenzene dichloride. After being kept at 0°C for 2 hours, the reaction mixture was chromatographed on a silica gel (5 g) column with a 1: 1 mixture of benzene - acetone as eluent. The fractions which showed a UV-absorbing spot at Rf 0.44 on a silica gel TLC plate (benzene - acetone, 1: 1) were evaporated *in vacuo* to dryness to provide 15 mg of 6-(1-acetoxyethyl)-3-chloro-3-isopropylidenepantetheinyl-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylic acid *p*-nitrobenzyl ester *S*-oxide (**8**).

8: IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1782 (β-lactam), 1740 (ester), 1665 (amide): UV $\lambda_{max}^{CH_2Cl_2}$ nm (ε) 267 (10,700): NMR ($CDCl_3$) δ 0.94 (3H, s), 1.01 (3H, s), 1.24 (3H, d, J=7.0 Hz), 1.38 (3H, s), 1.41 (3H, s), 2.04 (3H, s), 2.10~2.50 (3H, m), 2.70~3.90 (10H, m), 4.00 (1H, s), 4.08~4.45 (1H, m), 4.97 (1H, s), 5.18 (2H, s), 5.28~5.60 (1H, m), 6.48 (1H, br), 6.90 (1H, br), 7.49 (2H, d, J=9.0 Hz), 8.15 (2H, d, J=9.0 Hz): FD-MS (*m/z*) 745, 743 (M+1), 707 (M−Cl).

Elimination of Hydrochloride from **8**

A solution of 7.9 mg of **8** and 4 μl of triethylamine in 1.5 ml of benzene was stirred at room temperature for 30 minutes. The reaction mixture was charged on a silica gel (2.5 g) column and eluted with a 1: 3 mixture of benzene - acetone. All fractions were monitored by silica gel TLC using a 1: 1 mixture of benzene - acetone. Fractions containing a UV-absorbing material of Rf 0.11 were collected. Removal of the solvent by evaporation gave 5.7 mg of 6-(1-acetoxyethyl)-3-isopropylidenepantetheinyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid *p*-nitrobenzyl ester *S*-oxide (**9**).

9: IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1785 (β-lactam), 1735, 1710 (ester), 1660 (amide): UV $\lambda_{max}^{CH_2Cl_2}$ nm (ε) 310 (7,200), 269 (12,600): NMR ($CDCl_3$) δ 0.93 (3H, s), 1.00 (3H, s), 1.37 (3H, s), 1.37 (3H, d, J=7.0 Hz), 1.42 (3H, s), 2.02 (3H, s), 2.41 (2H, t, J=6.5 Hz), 2.80~3.90 (11H, m), 4.02 (1H, s), 4.20~4.55 (1H, m), 5.10~5.40 (3H, m), 6.54 (1H, br), 6.93 (1H, br), 7.58 (2H, d, J=8.5 Hz), 8.17 (2H, d, J=8.5 Hz).

Replacement of **9** with Thiophenol

A solution of 9.5 mg of the sulfoxide **9** in 2 ml of dry dimethylformamide was mixed at −50°C with triethylamine (2.8 μl) and thiophenol (1.7 μl) and allowed to stand at the same temperature for 15 minutes. After dilution with benzene, the organic solution was washed with 0.1 M phosphate buffer, pH 6.8, and then dried over anhydrous sodium sulfate. The evaporation residue was subjected to silica gel (5 g) column chromatography using a 15: 1 mixture of benzene - acetone as eluent. By silica gel TLC monitoring, fractions showing a UV-absobing spot at Rf 0.38 (benzene - acetone, 10: 1) were collected and concentrated *in vacuo* to dryness to yield 3.4 mg of 6-(1-acetoxyethyl)-7-oxo-3-phenylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid *p*-nitrobenzyl ester (**10**).

10: IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1780 (β-lactam), 1735, 1700 (ester): NMR ($CDCl_3$) 1.28 (3H, d, J=6.0 Hz), 2.10 (3H, s), 2.39 (1H, dd, J=19.0, 10.5 Hz), 2.72 (1H, dd, J=19.0, 8.0 Hz), 3.59 (1H, t, J=6.0 Hz), 4.13 (1H, ddd, J=6.0, 10.5, 8.0 Hz), 5.18 (1H, dq, J=6.0, 6.0 Hz), 5.26 (1H, d, J=14.0 Hz), 5.50 (1H, d, J=14.0 Hz), 7.15~7.60 (5H, m), 7.60 (2H, d, J=9.0 Hz), 8.18 (2H, d, J=9.0 Hz): EI-MS (*m/z*) 482 (M), 440 (M−CH_2=C=O).

Treatment of **3** with 1,5-Diazabicyclo[5.4.0]undec-5-ene (DBU)

DBU (4.8 μl) was added at 0°C to a solution of 10 mg **3** in 1 ml methylene chloride and agitated at

room temperature for 4 hours. Silica gel column chromatography provided 4.8 mg of a compound which had the same Rf value as **3** on a silica gel TLC plate. By NMR spectrometry, no epimerization at C-2 was observed in the product, while the hydrogen atom at C-6 was slightly epimerized.

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