CONVERSION OF OA-6129 B_2 INTO (5*R*,6*R*)-6-[(*R*)-1-FLUOROETHYL]-7-OXO-3-[(*N*,*N*,*N'*-TRIMETHYLCARBAMIMIDOYL)METHYL]THIO-1-AZABICYCLO[3.2.0]HEPT-2-ENE-2-CARBOXYLIC ACID (88617)†

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Since the epoch-making discovery of thienamycin[2], a number of extensive studies have been carried out on the development of clinically useful carbapenem compounds. As a result, formimidoylthienamycin (imipenem) has recently been put on the market as a combination drug (Primaxin)[3] with cilastatin, a renal dehydropeptidase-I inhibitor[4]. It has, however, a shortcoming in that its poor solubility in water[5], limits its clinical use to infusion.

MAK and FLIRI have succeeded in the total synthesis of novel 8-fluorinated carbapenem derivatives as racemates[1] *via* the Melillo lactone[6]. Among them, 88617 is most promising by virtue of excellent antimicrobial activity, improved resistance to dehydropeptidase-I and high physico-chemical stability. Subsequent biological evaluation studies, however, indicated that the optical activity of 8-fluoro carbapenem derivatives was critically important for expression of the desirable antimicrobial and enzymological profiles[7].

In the meanwhile, a series of OA-6129 carbapenems which are characterized by the C-3 pantetheinyl side chain are produced by a streptomycete[8]; and a selective fermentation method of OA-6129 B_2 which has a 1-hydroxyethyl side chain at C-6 became available by mutagenesis of specifically-blocked strains[9]. As the absolute configuration of the hydroxyl group is *S* in the C-6 side chain of OA-6129 B_2, it was thought that optically active 88617 could be prepared efficiently from OA-6129 B_2 by an *S*-oxide replacement reaction[10], if fluorination at C-8 proceeded under perfect inversion.

This paper describes the efficient conversion of OA-6129 B_2, a fermentation carbapenem product, into optically active 88617, an 8-fluorinated carbapenem derivative which improved antimicrobial activity and dehydropeptidase-I stability.

Treatment of OA-6129 B_2 sodium salt **1** with *p*-nitrobenzyl (*p*NB) bromide or pivaloyloxymethyl chloride in DMF gave *p*NB ester **2** or pivaloyloxymethyl (POM) ester **3** of OA-6129 B_2 (Fig. 1). The two hydroxyl groups in the pantoyl moiety of OA-6129 B_2 were protected by isopropylidenation for differentiation from the C-8 hydroxyl group.

The protected compound **4** or **5** was allowed to react with 1.2 equiv of diethylaminosulfur trifluoride (DAST)[11] at $-68°C$ in methylene chloride for 10 minutes. After the reaction mixture was diluted with methylene chloride and washed with a saturated aqueous sodium bicarbonate solution, silica gel column chromatography of the organic layer provided the desired fluorinated compound **6** or **7** having a fluorine atom in the *R* configuration at C-8 in 43 or 49% yield, respectively. No epimer at C-8 was observed at all in these reaction conditions.

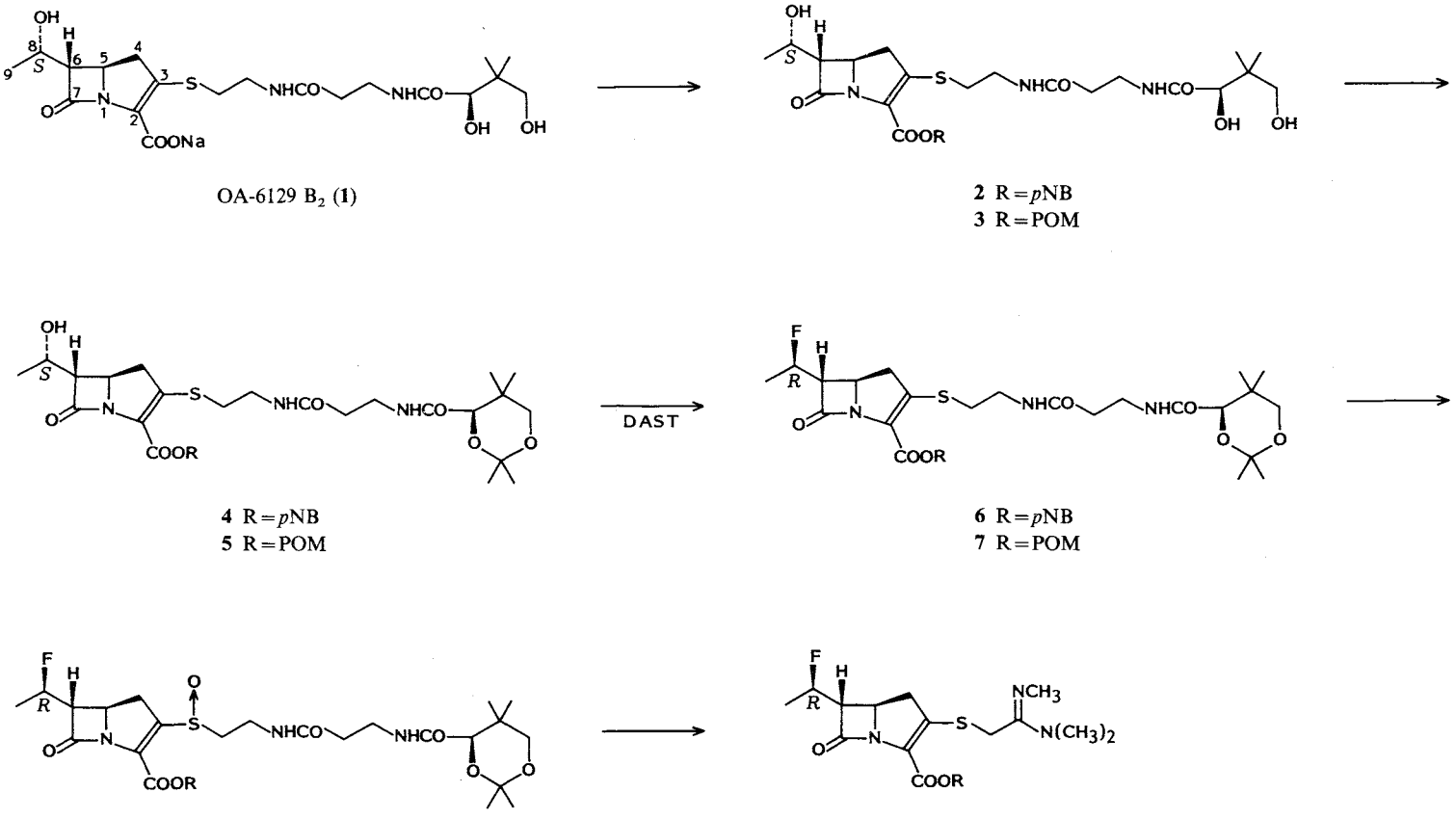
On the other hand, Ishikawa reagent (a mixture of diethylaminohexafluoropropane and diethylaminopentafluoropropene)†† with which it has been confirmed that fluorination proceeds by perfect inversion in the case of non-fused azetidinones (WATANABE, A. *et al.*; unpublished results), was also tested for stereospecific fluorination. However, treatment of **4** with 1.0 mol equiv of Ishikawa reagent afforded fluorinated compounds in 30% yield as a 1:1 mixture of the 8*R* and 8*S* epimers; (coupling constants $J_{6,8}=7.3$ Hz, $J_{8,F}=48.5$ Hz, $J_{8,9}=6.4$ Hz for 8*R*, $J_{6,8}=6.5$ Hz, $J_{8,F}=46.2$ Hz, $J_{8,9}=6.5$ Hz, for 8*S*); the ethylidene compound at C-6 was also produced in 10% yield. From these findings, it is concluded that DAST is better than Ishikawa reagent for the stereospecific fluorination of 8-hydroxycarbapenem compounds.

The fluorinated derivative **6** or **7** was oxidized with *m*-chloroperbenzoic acid in methylene chloride at $-20\sim0°C$ to give the corresponding *S*-oxide **8** or **9** in 76 or 73% yield. **8** or **9** was treated with α-mercapto-*N*,*N*,*N'*-trimethylacetoamidine nonafluorobutanesulfonate or its hydrochloride, providing the *p*NB ester nonafluorobutanesulfonate **10** in 40% yield or the POM ester hydrochloride **11** in 56% yield after CM-Sephadex C-25 column chromatography. The physico-chemical properties of the

† See ref 1.

†† Ishikawa reagent was purchased from Tokyo Kasei Kogyo Co., Ltd.

Fig. 1. Conversion of OA-6129 B_2 into 88617.



sulfonate **10**: MP 140~142.5°C; $[\alpha]_D^{23}$ +25.3° (*c* 0.975, CH_2Cl_2); UV $\lambda_{max}^{CH_2Cl_2}$ nm (ε) 269.5 (14,000), 312.5 (14,600); IR ν_{max}^{KBr} cm^{-1} 1775 (β-lactam); ^1H NMR ($CDCl_3$ + a few drops of DMSO-d_6) δ 1.43 (3H, dd, *J*=6.3 and 24.0 Hz, 9-H), 3.19 (3H, s, NCH_3 or $=NCH_3$), 3.30 (6H, s, $=NCH_3$ and NCH_3 or $N(CH_3)_2$), 3.3~3.8 (3H, m, 4-H and 6-H), 4.18 (2H, s, SCH_2), 4.33 (1H, m, 5-H), 4.6~5.4 (1H, m, 8-H), 5.20 (1H, d, *J*=14.1 Hz, C*H*H-Ar), 5.47 (1H, d, *J*=14.1 Hz, CH*H*-Ar), 7.62 (2H, d, *J*=9.0 Hz, Ar), 8.17 (2H, d, *J*=9.0 Hz, Ar), 8.3~8.9 (1H, br, SO_3H) were in good accordance with those of the authentic sample† synthesized by resolution of the Melillo lactone. Compound **10** was hydrogenated over 10% Pd-C in a mixture of ethyl acetate and 0.15 M MOPS buffer, pH 7.5, and purified by column chromatography on QAE-Sephadex A-25 and Diaion CHP-20 P to give 88617 in 43% yield as colorless crystals from ethanol.

Using a similar procedure, 8-fluorinated carbapenem derivatives having a variety of C-3 side chains were prepared. Their structure-activity relationships will be discussed in a separate paper.

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† The authentic sample of **10** was kindly supplied by Sandoz Company.