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SYNTHESIS OF A NOVEL C-6 NITROGEN-SUBSTITUTED CARBAPENEM FROM 6-AMINOPENICILLANIC ACID

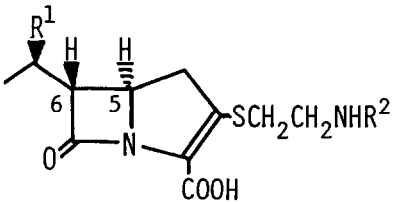
Kenichi Yamamoto, Masayoshi Nishino, Yasuyuki Kato,
Takeo Yoshioka, Yasutaka Shimauchi and Tomoyuki Ishikura

Sanraku-Ocean Co., Ltd., Central Research Laboratories,
Johnan 4-chome, Fujisawa 251, Japan

ABSTRACT: Synthesis of optically active 6-phthalimidocarbapenems from 6-aminopenicillanic acid is described.

Carbapenem compounds, a novel family of beta-lactam antibiotics, have recently drawn a world-wide attention as chemotherapeutics of a new generation, because they have a very wide spectrum of potent antibacterial activity covering Gram-negative bacteria. Carbapenem compounds are characterized by the carbon substituents at C-6(for example, hydroxyethyl in thienamycin 1[1]) and ethyl in PS-5 2[2]) instead of acylamino groups in conventional beta-lactams. A huge amount of information concerning the structure-antimicrobial activity relationships of penicillins and cephalosporins clearly indicates that the type and nature of side chains at C-6 of penicillins and C-7 of cephalosporins are critically important for the expression of antimicrobial activity. For example, acylamino groups are antimicrobially superior to carbon side chains.[3,4] Therefore, in the same line of approach, the introduction of substituted amino groups at C-6 of carbapenems is worth examining in view of modification of the chemical and biological properties of carbapenem compounds.

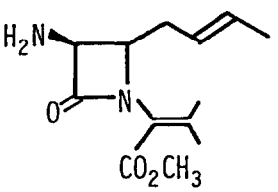
In this communication we describe the synthesis of 6-phthalimide-substituted carbapenems.



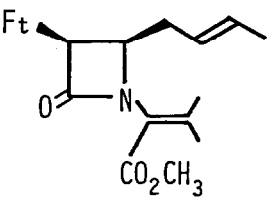
R^1: OH, R^2: H THIENAMYCIN 1

R^1: H, R^2: $COCH_3$ PS-5 2

According to the procedure of Onoue et al.;[5] 6-aminopenicillanic acid was converted to a diastereomeric mixture of 3-aminoazetidinones 3 and 4.



3 4α-H
4 4β-H



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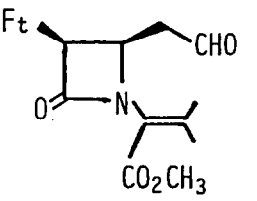

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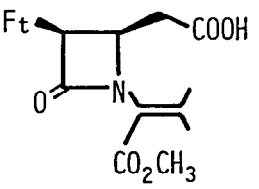

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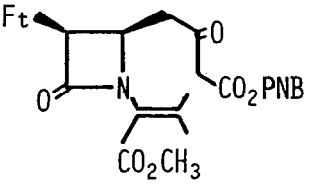

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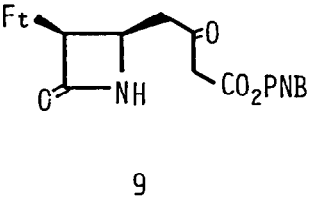

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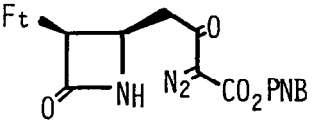
Ft : phthalimido
PNB : p-nitrobenzyl



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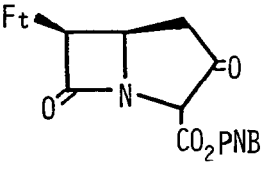

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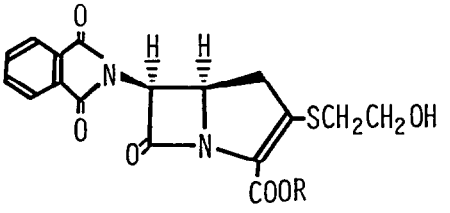
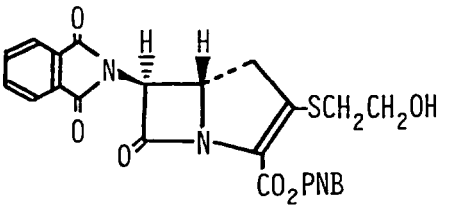


12 R: PNB
13 R: Na



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Phthalimidoazetidinone 5 was obtained by overnight reaction of 3, one of the diastereomers, with N-carboethoxyphthalimide in aqueous acetone containing sodium bicarbonate at room temperature. Ozonolysis of 5 in dichloromethane at -78°C for 5 min followed by dimethylsulfide treatment gave aldehyde 6 in 85% yield. By Jones oxidation at 0°C for 20 min in acetone, aldehyde 6 was converted into carboxylic acid 7 which was treated with N,N-carbonyldiimidazole at 25°C for 6 hr in tetrahydrofuran(THF) under nitrogen atmosphere. The resulting imidazolide was allowed to react with the magnesium salt of mono-p-nitrobenzyl ester of malonic acid in THF at 25°C for 16 hr under nitrogen atmosphere,[6] providing ketoester 8 in 45% yield. Compound 8 in dichloromethane was ozonized at -78°C for 10 min, and then treated with dimethylsulfide to give an ozonolysis product which, without preliminary isolation, was subjected to methanolysis for 10 min in boiling aqueous methanol, providing ketoester 9 in 93% yield.

The construction of the bicyclic ring system was achieved by the carbene insertion reaction.[7] Diazoketoester 10, a carbene precursor, was prepared by the reaction of 9 with p-toluenesulfonyl azide in acetonitrile containing triethylamine for 3 hr at room temperature. Subsequent treatment of 10 in benzene at 50°C for 20 min with a catalytic amount of rhodium(II) acetate under nitrogen atmosphere resulted in the formation of bicyclic ketoester 11. Without purification because of chemical instability, 11 was coverted to carbapenem 12[8] in 40% yield by treatment with diphenyl chlorophosphate in acetonitrile containing diisopropyl ethylamine at 0°C for 30 min under nitrogen atmosphere, followed by overnight reaction at 5°C with mercaptoethanol in the presence of diisopropyl ethylamine.

The protecting p-nitrobenzyl group in 12 was removed by hydrogenolysis using platinum dioxide at room temperature for 2 hr in THF-0.01M phosphate buffer, pH 8.0, at a hydrogen pressure of 4 kg/cm^2. Column chromatographic purification on QAE-Sephadex and Diaion HP20AG afforded the sodium salt of carbapenem carboxylic acid 13.[9]

Compound 14,[10] the diastereomer of 12, was also prepared in the similar manner, starting from the other isomeric aminoazetidinone 4.

The *in vitro* antimicrobial activity of carbapenem 13 was found to be moderate, whereas compound 14 having the unnatural configuration at C-5 was inactive on assay agar plates of test microorganisms containing horse serum.

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8. Physical data of 12: NMR($CDCl_3$) δ ppm 2.93(2H, t, J=6 Hz, SCH_2CH_2OH), 2.97(1H, dd, J=10, 18 Hz, C-4H), 3.22(1H, dd, J=8, 18 Hz, C-4H), 3.42(2H, t, J=6 Hz, SCH_2CH_2OH), 4.53(1H, m, C-5H), 5.23(1H, d, J=14 Hz, CHHAr), 5.50(1H, d, J=14 Hz, CHHAr), 5.74(1H, d, J=6 Hz, C-6H), 7.60(2H, d, J=9 Hz, ArH), 7.36-7.87(4H, m, ArH), 8.15(2H, d, J=9 Hz, ArH): IR($CHCl_3$, cm^{-1}) 1795, 1780, 1725, 1700(sh.), 1525, 1385: UV $\lambda_{max}^{CHCl_3}$ nm 323, 306, 271: $[\alpha]_D^{22}$ -108.3°(c 1.0, $CHCl_3$): High mass(m/z) 509.0866(calcd. for $C_{24}H_{19}N_3O_8S$ 509.0890).
9. Spectra data of 13: NMR(D_2O) δ ppm 3.00(2H, t, J=6 Hz, SCH_2CH_2OH), 3.13(2H, d, J=10 Hz, C-4H), 3.80(2H, t, J=6 Hz, SCH_2CH_2OH), 4.70(1H, m, C-5H), 5.39(1H, d, J=6 Hz, C-6H), 7.95(4H, m, ArH): UV $\lambda_{max}^{H_2O}$ nm(ε) 300.5(11900).
10. Physical data of 14: NMR($CDCl_3$) δ ppm 3.03(2H, t, J=6 Hz, SCH_2CH_2OH), 3.33(2H, d, J=9 Hz, C-4H), 3.82(2H, t, J=6 Hz, SCH_2CH_2OH), 4.57(1H, dt, J=3, 9 Hz, C-5H), 5.23(1H, d, J=14 Hz, CHHAr), 5.28(1H, d, J=3 Hz, C-6H), 5.48(1H, d, J=14 Hz, CHHAr), 7.65(2H, d, J=9 Hz, ArH), 7.60-7.85(4H, m, ArH), 8.18(2H, d, J=9 Hz, ArH): IR($CHCl_3$, cm^{-1}) 1780(broad), 1725, 1700(sh.), 1520, 1390: UV $\lambda_{max}^{CHCl_3}$ nm 325, 307, 271: High mass(m/z) 509.0887(calcd. for $C_{24}H_{19}N_3O_8S$ 509.0890).

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