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NOVEL TRANSFORMATION OF PENICILLIN INTO PENEM NUCLEUS : SYNTHESIS OF 2-CARBOXYLPENEM DERIVATIVE

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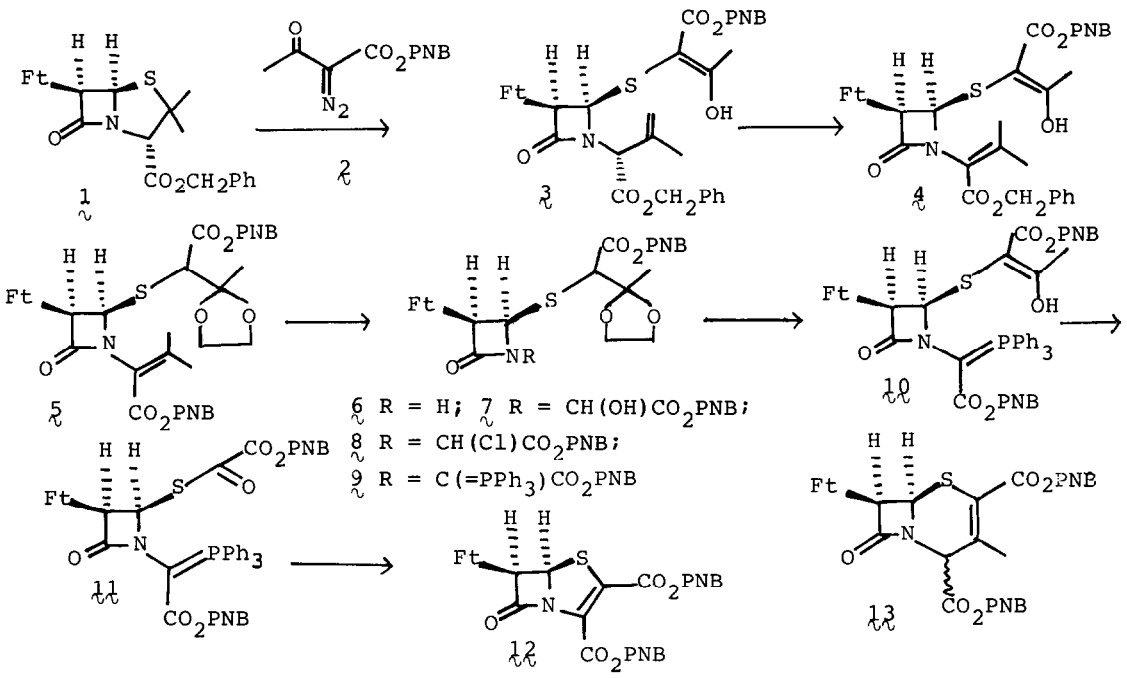
Summary —— A novel transformation of 6-aminopenicillanic acid (6-APA) into penem derivative is described.

We have recently succeeded in the conversion of a 6-aminopenicillanic acid into cephem derivative utilizing a carbene reaction of α-diazomalonate. In conjunction with the synthesis of new derivatives of cephems and penems, we have been interested in the efficient conversion of penicillin nucleus into penem derivative which bears a functional group at the C_2-position. It has been suggested by us[2] and others[3,4] that a carbene reaction would provide one of the most promising pathway to synthesize a functionalized 1,2-secopenicillin from penicillin. Our design for the conversion of a penicillin into a penem derivative involves a carbene reaction of α-diazoacetoacetate with 6-APA derivative as a key reaction.

The reaction of the benzyl 6-phthalimidylpenicillanate (1) with p-nitrobenzyl α-diazoacetoacetate (2) in benzene-methylene chloride (1 : 1 v/v) in the presence of rhodium acetate gave rise to the 1,2-secopenicillin derivative (3), whose treatment with triethylamine gave the conjugated ester (4) (79 % yield from 1). After ketalization of 4 with ethylene glycol and p-toluenesulfonic acid, the ketal (5) was treated with potassium permanganate to afford the azetidinone (6) (21 % yield[6] from 4). Introduction of C_2 unit at the N_1-position was carried out by the adoption of Woodward's procedure[5] to give the phosphorane (9) via the alcohol (7) and the chloride (8). Deprotection of the ketal group with perchloric acid furnished the β-keto ester (10) in 80% yield, which was ozonized in methylene chloride in the presence of trifluoroacetic acid to give the phosphorane (11). Heating 11 at 80°C in benzene brought about intramolecular Wittig cyclization to yield the penem (12) (42.7 % yield from 10).

Thus, we have succeeded in the conversion of a penicillin to a penem derivative which bears a functional group at the C_2-position, efficiently.

Moreover, the synthesis of a cephem ring system from 10 by an intramolecular Wittig cyclization afforded a ceph-2-em derivative (13) instead of an expected ceph-3-em derivative.



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(6) This yield was not optimized.

(7) All new compounds exhibited satisfactory spectroscopic and analytical data consistent with the structures. (12) : IR $\nu_{max.}$ ($CHCl_3$) 1820, 1780 and 1735 cm^{-1} (C=O); NMR ($CDCl_3$) δ 5.33 (2H, s, CH_2Ar), 5.40 (2H, s, CH_2Ar), 6.10 (1H, d, J = 4.2 Hz, C_5-H) and 6.16 (1H, d, J = 4.2 Hz, C_6-H); (13) IR $\nu_{max.}$ ($CHCl_3$) 1800, 1780, 1735 (C=O) and 1355 cm^{-1} (NO_2); NMR δ ($CDCl_3$) 2.29 (1.5H, s, 1/2 CH_3), 2.41 (1.5H, s, 1/2 CH_3), 4.37 (0.5H, s, C_4-H), 5.05 (1H, d, J = 7 Hz, C_6-H), 5.74 (0.5H, d, J = 4 Hz, 1/2 C_7-H), 5.84 (0.5H, d, J = 4 Hz, 1/2 C_7-H).

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