SYNTHESIS OF 2-CARBOXYLCEPHEM DERIVATIVE FROM 6-AMINOPENICILLANIC ACID

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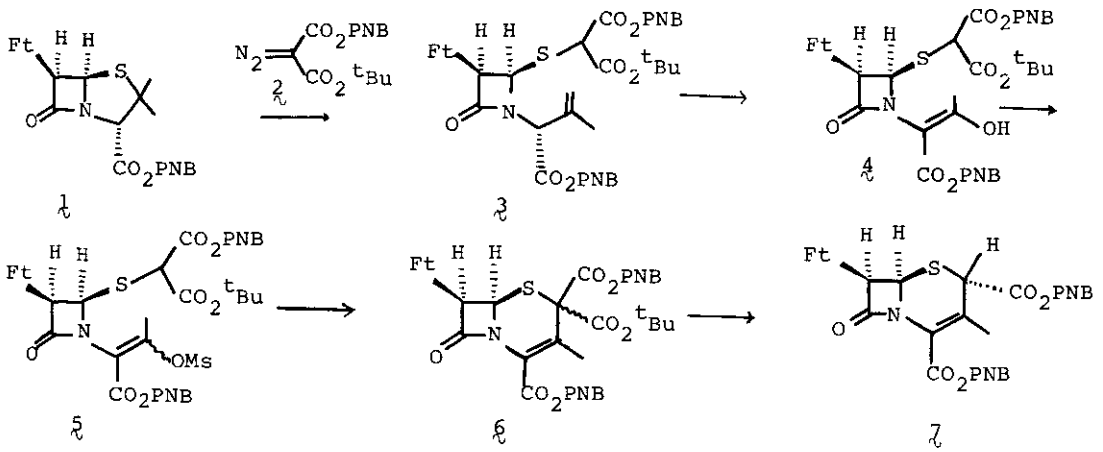
Abstract —— 6-Aminopenicillanic acid (6-APA) has been converted into 2α-carboxycephem derivative by a carbene insertion reaction, followed by Michael reaction.

Synthesis of new derivatives of cephem and penem antibiotics has recently attracted a considerable interest[1-7] owing to their potent antibacterial activity, though non-classical carbapenem or carbacephem antibiotics has been discovered. Among the various syntheses of cephem derivatives, much attention has been focused on the chemical modifications of the amino-function at the C_7-position and of acetoxymethyl-function at the C_3-position[8]. Interest in the synthesis of 2-substituted cephem antibiotics arose from their expected biological activity and oral use[9]. We here wish to report an efficient synthesis of 2α-carboxycephem derivative by a carbene reaction with 6-APA derivative. The transformation of 6-APA into cephem nucleus via 1,2-secopenicillin using a carbene reaction has originally been reported by Sankyo group[10] and the similar conversion to cephem by a nitrene reaction has been published by Takeda group[11]. Our synthesis of 2α-carboxylated cephem (7) began with the preparation of the corresponding 1,2-secopenicillin (3).

Thus, p-nitrobenzyl 6-phthalimidylpenicillanate (1) was treated with t-butyl p-nitrobenzyl α-diazomalonate (2) in benzene-CH_2Cl_2 (1 : 1 v/v) in the presence of $Rh_2(OAc)_4$ to give the 1,2-secopenicillin derivative (3) in 83 % yield. Ozonolysis of 3, followed by treatment with Me_2S, resulted in the formation of the β-keto ester (4) in 95 % yield, whose ring closure to the cephem (6) was achieved by Michael reaction of the mesylate (5) with 1,4-diazabicyclooctane (DABCO) in Me_2NCHO in 23 % yield. Since 6-APA was successfully converted to the cephem nucleus, the mono-decarboxylation of 6 was carried out by treatment with CF_3CO_2H in CH_2Cl_2 to give the diester (7)[12] as a single stereoisomer in 79 % yield. The stereochemistry of the ester group at the C_2-position was tentatively assigned to be α by its NMR spectral data[13].

Thus, we could synthesize the 2-carboxylcephem ring system from 6-APA efficiently by a carbene reaction, followed by Michael reaction, and a variety of 2-functionalized cephem derivatives would be synthesized by use of this approach.



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