

SYNTHESIS OF 2-CARBOXYLCEPHEM DERIVATIVE FROM 6-AMINOPENICILLANIC
ACID

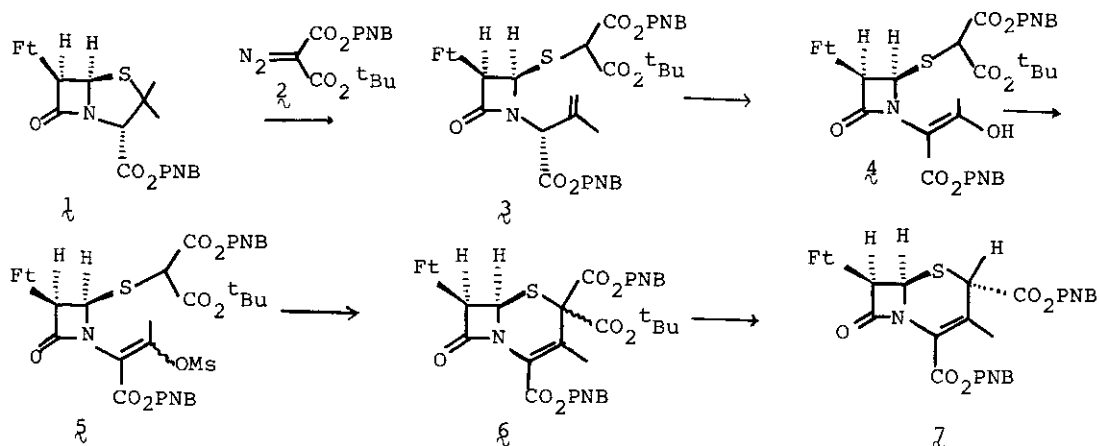
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Abstract — 6-Aminopenicillanic acid (6-APA) has been converted into 2 α -carboxycephem derivative by a carbene insertion reaction, followed by Michael reaction.

Synthesis of new derivatives of cephem and penem antibiotics has recently attracted a considerable interest¹⁻⁷ 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 C₇-position and of acetoxymethyl-function at the C₃-position⁸. Interest in the synthesis of 2-substituted cephem antibiotics arose from their expected biological activity and oral use⁹. We here wish to report an efficient synthesis of 2 α -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 group¹⁰ and the similar conversion to cephem by a nitrene reaction has been published by Takeda group¹¹. Our synthesis of 2 α -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-CH₂Cl₂ (1 : 1 v/v) in the presence of Rh₂(OAc)₄ to give the 1,2-secopenicillin derivative (**3**) in 83 % yield. Ozonolysis of **3**, followed by treatment with Me₂S, resulted in the formation of the β -keto ester (**4**) in 95 % yield, whose ring closure to the cephem (**5**) was achieved by Michael reaction of the mesylate (**5**) with 1,4-diazabicyclooctane (DABCO) in Me₂NCHO in 23 % yield. Since 6-APA was successfully converted to the cephem nucleus, the mono-decarboxylation of **5** was carried out by treatment with CF₃CO₂H in CH₂Cl₂ to give the diester (**7**)¹² as a single stereoisomer in 79 % yield. The stereochemistry of the ester group at the C₂-position was tentatively assigned to be α by its NMR spectral data¹³.

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.



References

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