FACILE SYNTHESIS OF CARBAPENEM ANTIBIOTICS. THE FIRST AND SIMPLE
STEREOSELECTIVE SYNTHESIS OF ANTIBIOTIC PS-5 BENZYL ESTER

Tetsuji Kanetani, Toshio Honda, Atsushi Nakayama, and Keiichiro
Fukumoto
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980,
Japan

Abstract — Antibiotic PS-5 benzyl ester was stereoselectively
synthesized by using a new carbon-carbon bond formation reaction
at the C-4-position of azetidin-2-one, as a key reaction.

Antibiotic PS-5, isolated from the fermentation broth of a soil microorganism,
Streptomyces cremeus subsp. aurantius A271 (ATCC 31358) and
Streptomyces fulvoviridis A 933, is a new β-lactam antibiotic, whose full structure has recently been report-
ed by the Sanraku Ocean group 3 to be as represented by 1. Antibiotic PS-5 displays
a broad spectrum of antibacterial activity against Gram-positive bacteria, including
β-lactamase-producing organisms.

Interest in the synthesis of new β-lactam antibiotics, such as thienamycin5-7, epi-
thienamycin8 and olivanic acids9-14 stems from their novel carbapenem ring system
and from their reported interesting biological activities. Efficient preparation of
these new β-lactams has recently received considerable attention. Though a number
of synthetic routes to thienamycin (2)15-20 have been reported during the past few
years, antibiotic PS-5 has not been synthesized to date. Here we would like to re-
port a short stereoselective synthesis of antibiotic PS-5 benzyl ester (3).

Scheme 1

\[ \begin{align*}
\text{1} & \quad R=H \\
\text{2} & \quad R=CH_2Ph
\end{align*} \]
The key reaction in this synthesis is a new carbon-carbon bond formation at the C₄-position of azetidin-2-ones. It being well known²¹ that the 4-acetoxy or 4-sulfonyl groups of azetidin-2-ones are readily displaced by sulfur, nitrogen and oxygen groups, we decided to investigate an analogous carbon displacement reaction. The development of a functionalized carbon displacement reaction at the C₄-position of azetidin-2-ones was therefore our first goal in antibiotic PS-5 synthesis. The enolate derived from ethyl acetate and lithium hexamethyl disilazide was treated with 4-acetoxy-azetidin-2-one (₃) in THF at -78° to afford ⁵ (15 %). Similarly, the enolate derived from dimethyl malonate reacted with ₃ to furnish ⁶ (21 %).

On consideration of the accepted reaction mechanism, i.e. Michael addition of enolate to the intermediate (⁷), it was expected that this reaction with 3-substituted azetidin-2-ones would lead to derivative with a trans-relationship between C₃ and C₄. 3-Ethyl- and 3-isopropylazetidin-2-ones were easily prepared as follows. n-Butyraldehyde (₈) was heated with acetic anhydride in the presence of sodium acetate (80°, 12 h) to afford the enol acetate (₉) ([E : Z = 3 : 2, 38 %], which was converted to the azetidin-2-one (₁₀) (trans : cis = 1 : 1) by treatment with chlorosulfonyl isocyanate (CSI), followed by reductive cleavage of the N-S bond, in 44 % yield from ₉. Isovaleraldehyde (₁₁) was also converted to ₃ (trans : cis = 1 : 1), via the enol acetate (₁₂) ([E : Z = 3 : 2], in a similar way. The above 3-ethylazetidin-2-one (₁₀) was treated with t-butyl α-diazoacetoacetate²² (₁₃) in the presence of lithium hexamethyl disilazide at -78° for 2 h, to afford ₁₄, in 12 % yield, IR (CHCl₃) 3430 (NH), 2170 (diaz), 1760, 1720, 1648 (C = O) cm⁻¹. In our synthetic scheme, the diazo group plays two important roles; in protection the active methylene during substitution, and in acting as carbene precursor in the subsequent insertion reaction. Thermal cyclization of ₁₄ in the presence of Rh₂(OAc)₄ in benzene furnished bicyclic ketoester (₁₅) in quantitative yield, IR (CHCl₃) 1770, 1735 (C = O) cm⁻¹; NMR δ (CDCl₃), 1.09 (3H, t, J = 7 Hz, -CH₂CH₃), 1.42 (9H, s, t-Bu), 3.87 (1H, dt, 

---1968---
The trans-configuration at C₅ and C₆ in 1₆ was determined from the NMR coupling constant, and the proposed reaction mechanism is therefore presumed correct. Introduction of the N-p-nitrobenzyloxy carbonyl cysteamine moiety to 1₆ was achieved by adoption of the Merck method, to give the antibiotic PS-5 derivative (1₆) approximately in 70% yield from 1₆, mp 124°C, IR (CHCl₃) 3425 (NH), 1770, 1720 (C=O), 1345 (NO₂) cm⁻¹; NMR (CDCl₃) 1.03 (3H, t, J = 7 Hz, -CH₂CH₃), 1.53 (9H, s, t-Bu), 1.77 (2H, br q, J = 7 Hz, -CH₂CH₃), 3.91 (1H, dt, J = 3 and 9 Hz, C₅-H), 5.16 (2H, s, -CH₂Ar), 5.39 (1H, br s, NH), 7.45 and 8.18 (each 2H, each d, J = 8 Hz, aromatic protons); m/e 491 (M⁺), 435, 364. In a similar manner, antibiotic PS-6 derivative (20) was synthesized in three steps, in 13% overall yield, from 1₅. The NMR spectrum of 20 exhibited the C₅-H resonance as a double triplet with J = 3 and 9 Hz at 5.91 ppm, which again indicated a trans-relationship between the C₅- and C₆-positions.

Finally, antibiotic PS-5 benzyl ester was synthesized by an analogous route in order to confirm the structures, including stereochemistry of our synthetic carbapenems (1₉ and 20). Thus the azetidin-2-one (1₉) was treated with benzyl a-diazoacetooacetate (21) to afford the benzyl ester (22), which was converted to the bicyclic ketoester (23). Introduction of the N-acetylcysteamine moiety, rather than N-p-nitrobenzyloxy carbonylcysteamine, furnished antibiotic PS-5 benzyl ester (3), the spectroscopic data of which were indistinguishable from those provided by Dr. T. Ishikura of the Sanraku Ocean group.

---1969---

---1969---

---1969---
Thus, carbapenem antibiotics of the PS-series have been stereoselectively synthesized using a new carbon-carbon bond formation reaction at the C4-position of azetidin-2-ones, and this reaction is expected to provide a useful synthetic pathway to other carbapenem antibiotics.

We thank Dr. T. Ishikura, Sanraku Ocean Co., Ltd., for providing various spectroscopic data on PS-5 antibiotic. We also acknowledge the assistance of the Central Analytical Laboratory of Tohoku University.

REFERENCES

Received, 9th September, 1980