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

Tetsuji Kametani*, Toshio Honda, Atsushi Nakayama, and Keiichiro Fukumoto

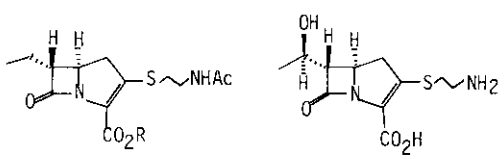
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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. auratilis A271 (ATCC 31358)[1] and Streptomyces fulvoviridis A 933[2], is a new β-lactam antibiotic, whose full structure has recently been reported 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.[4]

Interest in the synthesis of new β-lactam antibiotics, such as thienamycin[5-7], epithienamycin[8] and olivanic acids[9-14], 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 report a short stereoselective synthesis of antibiotic PS-5 benzyl ester (3).

Scheme 1

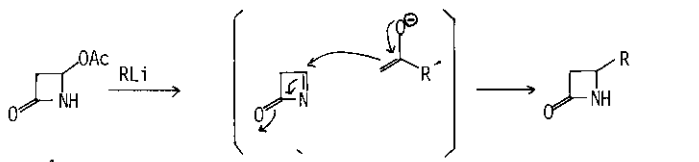


1 R=H
3 R=CH_2Ph

2

The key reaction in this synthesis is a new carbon-carbon bond formation at the C_4-position of azetidin-2-ones. It being well known[21] 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 C_4-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 (4) in THF at -78° to afford 5 (15 %). Similarly, the enolate derived from dimethyl malonate reacted with 4 to furnish 6 (21 %).

Scheme 2

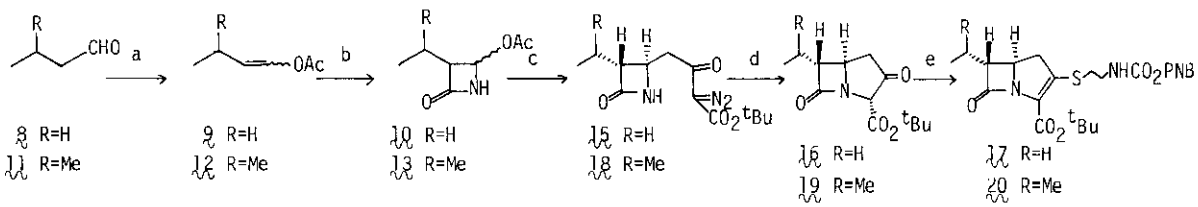


4 7 5 R=CH_2CO_2Et 6 R=$CH(CO_2Me)_2$

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 C_3 and C_4. 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 13 (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-diazoacetoacetate[22] (14) in the presence of lithium hexamethyl disilazide at -78° for 2 h, to afford 15, in 12 % yield, IR ($CHCl_3$) 3430 (NH), 2170 (diazo), 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 15 in the presence of $Rh_2(OAc)_4$[23] in benzene furnished bicyclic ketoester (16) in quantitative yield, IR ($CHCl_3$) 1770, 1735 (C = O)cm^{-1}; NMR δ ($CDCl_3$), 1.09 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$), 1.42 (9H, s, t-Bu), 3.87 (1H, dt,

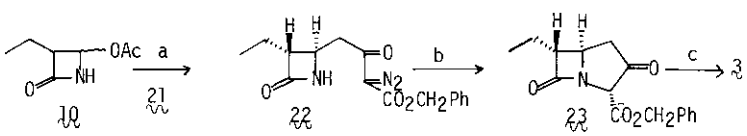
J = 2 and 7 Hz, C_5-H), 4.52 (1H, s, C_3-H). The trans-configuration at C_5 and C_6 in 16 was determined from the NMR coupling constant, and the proposed reaction mechanism is therefore presumed correct. Introduction of the N-p-nitrobenzyloxycarbonyl-cysteamine moiety[23] to 16 was achieved by adoption of the Merck method, to give the antibiotic PS-5 derivative (17) approximately in 70 % yield from 16, mp 124°C, IR ($CHCl_3$) 3425 (NH), 1770, 1720 (C = O), 1345 (NO_2)cm^{-1}; NMR δ ($CDCl_3$) 1.03 (3H, t, J = 7 Hz, $-CH_2CH_3$), 1.53 (9H, s, t-Bu), 1.77 (2H, br q, J = 7 Hz, $-CH_2CH_3$), 3.91 (1H, dt, J = 3 and 9 Hz, C_5-H), 5.16 (2H, s, $-CH_2Ar$), 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 13. The NMR spectrum of 20 exhibited the C_5-H resonance as a double triplet with J = 3 and 9 Hz at 3.91 ppm, which again indicated a trans-relationship between the C_5- and C_6-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 (17 and 20). Thus the azetidin-2-one (10) was treated with benzyl α-diazoacetoacetate (21) to afford tne benzyl ester (22), which was converted to the bicyclic ketoester (23). Introduction of the N-acetylcysteamine moiety[24], 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.



8 R=H, 11 R=Me; 9 R=H, 12 R=Me; 10 R=H, 13 R=Me; 15 R=H, 18 R=Me; 16 R=H, 19 R=Me; 17 R=H, 20 R=Me

a AcOH, NaOAc; b CSI, then Na_2SO_3 ; c $LiN(TMS)_2$, 14;
d $Rh_2(OAc)_4$; e $ClPO(OPh)_2$, $^iPr_2NEt$, DMAP, then HS∿$NHCO_2PNB$, $^iPr_2NEt$



10; 22; 23

a $LiN(TMS)_2$, 21 ; b $Rh_2(OAc)_4$; c $ClPO(OPh)_2$, $^iPr_2NEt$, DMAP, then HS∿$NHAc$, $^iPr_2NEt$

Thus, carbapenem antibiotics of the PS-series have been stereoselectively synthesized using a new carbon-carbon bond formation reaction at the C_4-position of azetidin-2-ones, and this reaction is expected to provide a useful synthetic pathway to other carbapenem antibiotics.

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