Tetrahedron Letters,Vol.26,No.39,pp 4739-4742,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

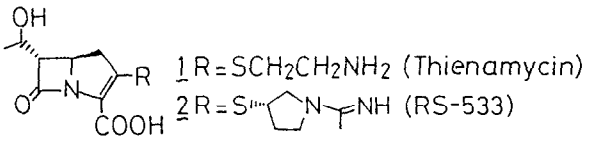
SYNTHETIC STUDY OF 1-SUBSTITUTED CARBAPENEM ANTIBIOTICS

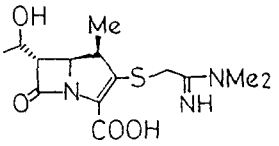
Tomoyuki Shibata, Kimio Iino, Teruo Tanaka, Toshihiko Hashimoto,
Yukiko Kameyama and Yukio Sugimura*

Chemical Research Laboratories, Sankyo Co., Ltd.,
Hiromachi, Shinagawa-ku, Tokyo, 140, Japan

Summary: Total synthesis of 1-substituted carbapenems is described. The key step is the reaction of acetoxyazetidinone (7) with ketene silyl acetal (8).

Since the discovery of thienamycin (1),[1] because of its high antibacterial activity and broad spectrum, carbapenem antibiotics have attracted much attention. But 1 is chemically unstable and readily metabolized by renal dehydropeptidase-I (DHP-I). In the previous paper,[2] we reported the synthesis of RS-533 (2) which is more potent in activity and more stable than 1. On the other hand, D.H.Shih *et al.* synthesized 1-β-methylcarbapenem 3 and found that introduction of a methyl substituent to the 1-positions of carbapenems was very effective in improving its metabolical stability.[3] We have also been interested in biological effect of some substituents introduced to the 1-position of RS-533. For the effective synthesis of 1-β-methylcarbapenems, stereoselective synthesis of β-Me isomer 6a(R^1=CH_3, R^2=H) is necessary as the key intermediate, but the Merck group's





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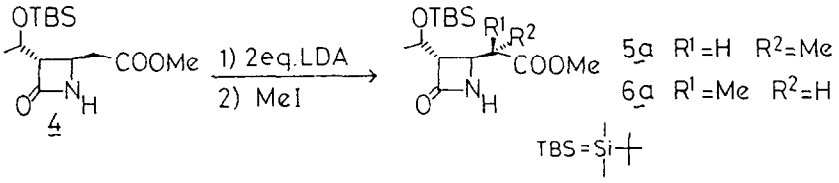
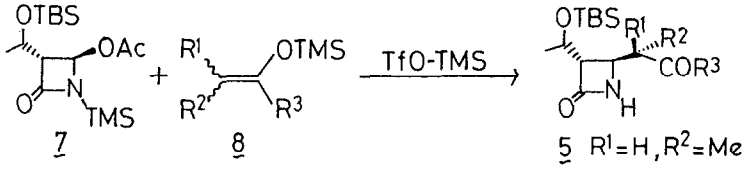


method (treatment of 4 with 2 equiv. of LDA and MeI) gave α-Me isomer (5a) as the major product (5a:6a=4:1).[3] We now report an improved method for the preparation of β-Me isomer 6 and the synthesis of 1-β- and 1-α-methyl RS-533 (17β and 17α) as well as other 1-substituted carbapenems.

The key step of our synthesis is the reaction of acetoxyazetidinone 7 with ketene silyl acetal 8 in the presence of trimethylsilyl trifluoromethanesulfonate (TfO-TMS).[4] The results are summarized in Table I.



5 R^1=H, R^2=Me
6 R^1=Me, R^2=H
9 R^1,R^2=OMe,H
10 R^1,R^2=Me,Me

Table I

The reactions of 7 with 8

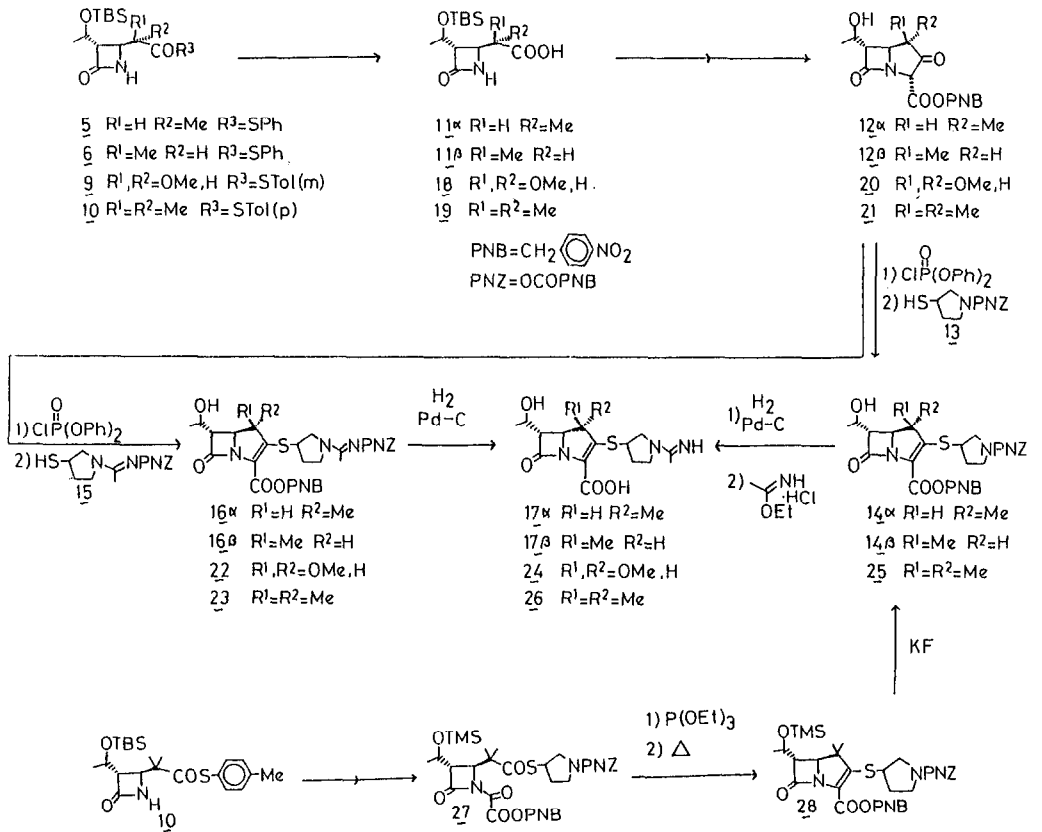
entry	8 R^1,R^2	R^3	product	yield
a	Me,H	OMe	5 and 6	94%(6/5=1/2.6)
b	Me,H	SPh	5 and 6	81%(6/5=1.6/1)
c	OMe,H	STol(*m*)	9	68%
d	Me,Me	OEt	10	96%
e	Me,Me	STol(*p*)	10	46%

Ketene silyl acetal 8a(R^1,R^2=Me,H;R^3=OMe) reacted with 7 in CH_2Cl_2 at room temperature in the presence of a catalytic amount of TfO-TMS to afford a mixture of α-Me isomer (5a(R^3=OMe), major) and β-Me isomer (6a(R^3=OMe), minor). On the other hand, ketene silyl acetal 8b(R^1,R^2=Me,H;R^3=SPh; E:Z=6:1) afforded β-Me isomer (6b(R^3=SPh)) as the major product along with α-Me isomer (5b(R^3=SPh)), these isomers being easily separated by silica gel chromatography or recrystallization. And 8b(E:Z=1:6) afforded a same result.

Compound 5b and 6b were separated by silica gel chromatography and were hydrolyzed (aq.NaOH in MeOH) quantitatively to give 11α and 11β, respectively. According to the Merck method,[3] 11α and 11β were converted to 1-α-methyl-2-ketocarbapenam (12α) and 1-β-isomer (12β), respectively. 1-β-Methyl-2-ketocarbapenem (12β) was readily converted to 14β by the condensation reaction with 3-(S)-mercaptopyrrolidine derivative (13) almost quantitatively, and gave 1-β-methyl RS-533 (17β)[6] after deprotection (PNB and PNZ) by catalytic hydrogenation (Pd-C in H_2O-THF) and successive treatment with ethoxyacetimidate in 57% yield.

On the other hand, the α-Me isomer (14α) obtained from 12α and 13 was very unstable and could not be isolated. So 12α was converted to 16α by the condensation reaction with (S)-mercaptoamidine derivative (15) (Y.43%). 16α Was more stable than 14α, and gave 1-α-methyl RS-533 (17α)[6] after deprotection by catalytic hydrogenation (Y.51%).

Analogously, 1-methoxy- (20) and 1,1-dimethyl-2-ketocarbapenams (21) were synthesized from 9(R^3=STol(*m*)) and 10(R^3=STol(*p*)), respectively. 20 Was readily converted to 22 (Y.quant.), which gave 1-methoxy RS-533 (24)[6] by catalytic hydrogenation (Y.21%). These 1-methoxy compounds (9, 18, 20, 22 and 24) could not be separated to give α- and β-isomers. On the other hand, 21 could not be converted to 23 or 25 owing to steric hindrance of the 1,1-dimethyl group. We, therefore, applied Oida's method[5] to 10, and synthesized 27. 27 Was cyclized *via* the intramolecular Wittig reaction to give 28 in 35% yield. 28 Was treated with KF in aq.CH_3CN to afford 25 and successive treatment with ethoxyacetimidate gave 1,1-dimethyl RS-533 (26)[6] in 18% yield.



1-β-Methyl RS-533 (17β) is highly resistant to enzymatic hydrolysis by DHP-I, and shows strong antibacterial activity and good bioavailability. 1-α-Methyl RS-533 (17α), 1-methoxy RS-533 (24) and 1,1-dimethyl RS-533 (26) are also rather resistant to DHP-I but showed relatively weak antibacterial activities. The detailed antibacterial activities of these 1-substituted RS-533 will be reported elsewhere.

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6. Spectra Data: 17α: UV λ_{max} 290nm(ε 4800); IR(KBr) 3400, 1765, 1685, 1635, 1600cm^{-1}; NMR(400MHz, in D_2O, ppm) 1.09(3H, d, J=7Hz), 1.16(3H, d, J=7), 1.8-2.0(1H,m), 2.07,2.08(each 1.5H, s), 2.1-2.3(1H,m), 3.05-3.2(1H,m), 3.2-3.95(7H,m), 4.0-4.1(1H,m). 17β: UV λ_{max} 297nm(ε 8700); IR(KBr) 3400, 1755, 1680, 1635, 1590cm^{-1}; NMR(400MHz, in D_2O, ppm) 1.04(3H, d, J=7), 1.10(3H, d, J=6), 1.85-2.05(1H,m), 2.05,2.09(each 1.5H, s), 2.25-2.4(1H,m), 3.15-3.95(7H, m), 4.0-4.15(2H,m). 24: UV λ_{max} 297nm(ε 5500); IR(KBr) 3330, 1765, 1675,1590cm^{-1}; NMR(400MHz, in D_2O, ppm) 1.13-1.18(3H,m), 1.87-2.02 (1H,m), 2.22-2.36(1H,m), 2.05,2.07,2.09,2.10(3H,each s), 3.29,3.31(3H,each s), 3.4-4.15(9H,m). 26: UV λ_{max} 280nm(ε 5300); IR(KBr) 3350, 1755, 1670, 1630, 1600cm^{-1}; NMR(90MHz, in D_2O, ppm) 0.92(3H,s), 1.09(3H, d, J=6Hz), 1.13(3H,s), 2.06(3H,s), 1.56-2.58(2H,m), 3.06-4.25(8H,m).

(Received in Japan 9 July 1985)