Tetrahedron Letters,Vol.25,No.44,pp 5075-5078,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

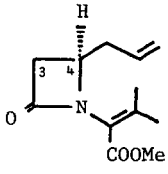
SYNTHETIC STUDIES ON CARBAPENEM ANTIBIOTICS FROM PENICILLINS. II[1]. REGIO- AND STEREOSELECTIVE ALDOL REACTION OF A CHIRAL AZETIDINONE: A SYNTHESIS OF OPTICALLY ACTIVE 6-EPICARPETIMYCINS[2].

Hideo Hirai[a], Kozo Sawada[a], Matsuhiko Aratani[b], and Masashi Hashimoto*[a]

Exploratory Research Laboratories[a], Central Research Laboratories[b],
Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-Ku, Osaka 532, Japan

Summary: Aldol and alkylation reactions of the chiral 4-allylazetidinone 1 gave 3,4-trans-azetidinones as major products, in which 10 was converted in several steps to the optically active 6-epicarpetimycins 2.

Considerable effort has been directed recently toward the total synthesis of chiral carbapenem antibiotics[3]. As part of our continuing program on ß-lactam antibiotics, we have concentrated on the synthesis of optically active carbapenems by utilization of the penicillin ß-lactam as a chiral precursor. In the preceding paper[1], we described the stereospecific synthesis of 4-allylazetidinones from penicillins, which allowed the introduction of the chiral functionality necessary for construction of the optically active carbapenem ring system. In most of the carbapenem antibiotics, the relative stereochemistry at C-3 and C-4 of the ß-lactam ring is trans except few examples of the cis stereochemistry in the case of such as carpetimycins[3f,4]. Accordingly, we then focused our attention on the introduction of alkyl side-chains at C-3 with trans stereochemistry to the ß-allyl substituent at C-4. Herein we report stereocontrolled aldol and alkylation reactions of allylazetidinone 1, which worked favorably to provide the key intermediates 10 for the synthesis of the 5,6-trans-carbapenem antibiotics. The feasibility of these reactions could be illustrated by a total synthesis of 6-epicarpetimycins 2[5], which is also the subject in this paper.



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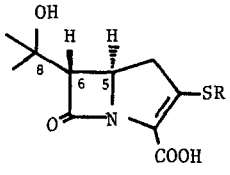
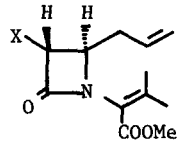


2

4-Allylazetidinone 1, the key precursor for the present investigation, was prepared from phthalimidoylazetidinone 3[1] as follows. Dephthalization of 3 using $Me_2N(CH_2)_3NH_2$ (CH_2Cl_2-MeOH, 45°C, 24h) gave aminoazetidinone 4 in 85% yield. Formylation of 4 (Ac_2O-HCO_2H, CH_2Cl_2, 0°C, 1h), followed by dehydration ($POCl_3$, 2,6-lutidine, CH_2Cl_2, 0°C, 3.5h) gave isocyanoazetidinone 6 via 5 in 74% yield. Subsequent radical reduction (*n*-Bu_3SnH, AIBN,

benzene, reflux, 20min)[6] gave 1[11] in 90% yield.

A trans introduction of the hydroxyethyl side chain on C-3 of ß-lactam ring had been achieved by the Merck group via an aldol reaction of acetonide 7[7]. In the case of 1 as an aldolization precursor, however, regiospecific enolization of the ß-lactam appeared to be somewhat tedious, because there might be occurred a competitive enolization of the α,β-unsaturated ester by treatment with a base. In fact, reaction of 1 using 1 equiv of lithium isopropylcyclohexylamide(LICA) in THF at -78°C, followed by treatment with DCl-D_2O afforded a mixture of the mono-deuterized product 8a(33 %) and its isomer 8'a(37 %)[8]. When this reaction was conducted using 3 equiv of LICA, the di-deuterized products 8b and 8'b were obtained in 37% and 47% yields, respectively. These results established that the α,β-unsaturated ester is more acidic than the ß-lactam carbonyl and the enolization at C-3 of the ß-lactam barely occurs by using the excess of the base, leading to the dianion enolate 9 in situ. We reasoned, therefore, that a kinetic aldol reaction of 9 using e.g. acetone as reagent would proceed in a regiospecific manner at C-3 on the ß-lactam to give the desired aldolization products 8c and 8'c. After some examinations, this reaction was best



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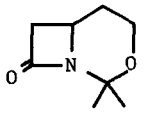

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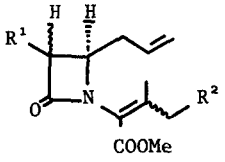

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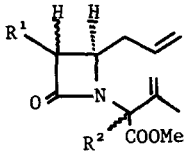


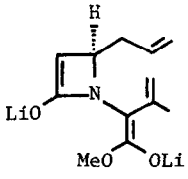
8'

3 X = 

4 X = $-NH_2$

5 X = -NHCHO

6 X = -NC



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a R^1=H, R^2=D

b R^1=R^2=D

c R^1=$-C(OH)Me_2$, R^2=H

d R^1=-CH(OH)Me, R^2=H

e R^1=Me, R^2=H

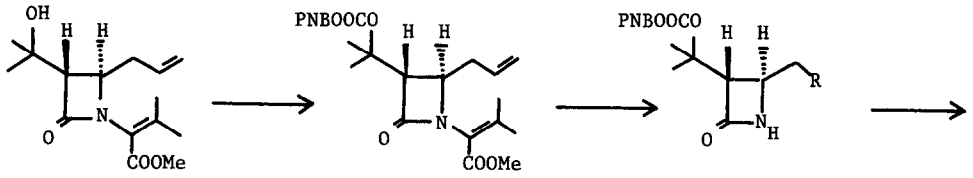
f R^1=Et, R^2=H

Table 1. Aldol and Alkylation Reactions of 1[a)]

Entry	LICA	Electrophile	Product	Isolation Yield trans	cis	Ratio (trans/cis)
1	2.7 eq	CH_3COCH_3 (1.5eq)	8c	58.8 %	21.3 %	2.8
2	3.0 eq	CH_3CHO (1.5eq)	8d	40.9 %	16.5 %	2.5[b)]
3	3.0 eq	CH_3I (4.0eq)	8e	32.3 %	12.1 %	2.7
4	3.0 eq	C_2H_5I (4.0eq)	8f	58.5 %[c)]		2.3[d)]

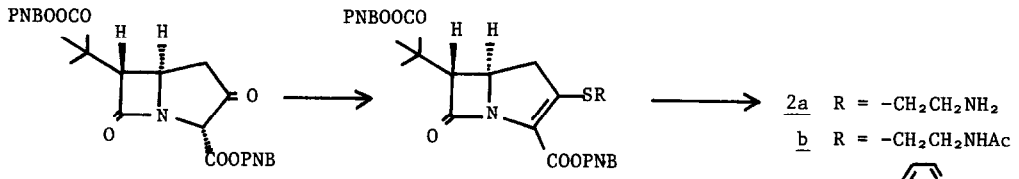
a) Reaction conditions for dianions formation: -78°C, 1h and -40°C, 20 min; aldol reactions: -78°C, 30min and -30°C ∿-20°C, 30min; alkylation reactions: -78°C, 30min and -30°C, 30min. b) The ratios of the 8R and 8S isomers: trans, 2:5; cis, 2:1. c) An attempt was unsuccessful for separation of the trans and cis products. d) The ratio was estimated on the 100MHz ^1H NMR spectrum.

achieved as follows. Treatment of 1 with 2.7 equiv of LICA in THF at -78°C for 1 h and -40°C for 20 min, followed by reaction with 1.5 equiv of acetone at -78°C for 30 min and -30 ∿-20°C for 30 min afforded, after quenching with acetic acid at -20°C and workup in the usual manner, the crude aldolization products as a mixture of 8c and the corresponding β,γ-isomer 8'c. For isomerization of 8'c to 8c, the crude mixture was treated with Et_3N (CH_2Cl_2, r.t., 2days) to furnish the thermodynamically stable 8c (two C-3 epimers)[9], which were separated by silica gel chromatography to give trans-azetidinone 10[11](58.8%) and its cis-isomer (21.3%). Aldol and alkylation reaction of 1 with other electrophiles (acetaldehyde, methyl iodide, and ethyl iodide) were also carried out under similar conditions to yield, as expected, the corresponding products 8d-f, respectively (see Table 1).



10 11

12 R = -COOH
13 R = -$COCH_2COOPNB$
14 R = -$COC(=N_2)COOPNB$



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16a R = -$CH_2CH_2NHCOOPNB$
b R = -CH_2CH_2NHAc
c R =

2a R = -$CH_2CH_2NH_2$
b R = -CH_2CH_2NHAc
c R = 

In order to demonstrate the feasibility of the above reactions for synthesis of the carbapenem antibiotics, we then exploited 10 for a synthesis of 6-epicarpetimycins 2. Protection of the hydroxy group of 10 with *p*-nitrobenzyl chloroformate (*n*-BuLi, THF, -78°C ∿ 0°C, 2.5h, 61%) to 11 was followed by Leumieux-Rudloff oxidation ($KMnO_4$, $NaIO_4$, acetone-phosphate buffer(pH 6.8), 17h, 64%) to produce carboxylic acid 12[11]. The acid 12 was converted by the Masamune's procedure[10](N,N'-carbonyldiimidazole, $Mg(O_2CCH_2CO_2PNB)_2$, THF, r.t., 17h) to ß-keto ester 13 in 78% yield. Transformation of 13 into 2 was achieved by employing the Merck method. Thus, diazotization of 13 with *p*-TsN_3 (Et_3N, CH_3CN, 0°C ∿r.t., 30min) afforded diazo ester 14, which was subsequently subjected to thermolysis ($Rh_2(OAc)_4$, benzene, reflux, 30min) to give bicyclic keto ester 15 in 95% yield. Activation of the carbonyl group in 15 ($(PhO)_2POCl$, *i*-Pr_2NEt, DMAP, CH_3CN, 0°C, 1h) and subsequent reaction with thiols (-15°C, 17h) yielded the protected 6-epicarpetimycins 16. Deprotection of 16 by hydrogenation (H_2(40psi), 5% Pd/C or PtO_2, 30% H_2O-dioxane, r.t., 2h), followed by chromatography on Dia-ion HP-20 AG column provided 6-epicarpetimycins 2.

6-Epicarpetimycin 2c[11] was found to have a strong ß-lactamase inhibitory activity, although its antibacterial activity was considerably less than the corresponding carpetimycin.

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9) Epimerization at C-3 of both 8 and 8' seemed not to occur under these conditions. See reference 4b and T. Kametani, S. P. Huang, T. Nagahara, and M. Ihara, J. Chem. Soc., Perkin I, 2282(1981).
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11) Compound 1: bp 93°C(0.07torr); IR(CH_2Cl_2) 1750, 1720cm^{-1}; H^1 NMR($CDCl_3$) 1.94(s, 3H), 2.18(s, 3H), 2.38(ddd, 2H, J=1.0, 7.0, and 14.0Hz), 2.64(dd, 1H, J=2.5 and 15.0Hz), 3.08(dd, 1H, J=5.5Hz and 15.0Hz), 3.72(s, 3H), 3.96(ddt, 1H, J=2.5, 5.5, and 7.0Hz), 4.4-5.2(m, 2H), 5.5-6.0(m, 1H). 10: IR(CH_2Cl_2) 1740, 1715cm^{-1}; ^{1}H NMR($CDCl_3$) 1.31(s, 3H), 1.38(s, 3H), 1.96(s, 3H), 2.81(s, 3H), 2.2-2.5(m, 3H), 2.90(d, 1H, J=3.0Hz), 3.76(s, 3H), 3.81(dt, 1H, J=3.7Hz), 4.9-5.2(m, 2H), 5.5-6.0(m, 1H). 12: IR(CH_2Cl_2) 1750, 1730, 1710 cm^{-1}; ^{1}H NMR(CD_3OD) 1.28(s, 3H), 1.32(s, 3H), 2.5-2.7(m, 2H), 2.90(d, 1H, J=2.5Hz), 3.8-4.0(m, 1H). 2c: IR(KBr) 3380, 1755, 1600, 1575, 1385cm^{-1}; ^{1}H NMR(D_2O) 1.32(s, 3H), 1.39(s, 3H), 2.91(d, 2H, J=9.0Hz), 3.48(d, 1H, J=3.0Hz), 4.26(dt, 1H, J=3.0 and 9.0Hz), 7.51(d, 2H, J=5.0Hz), 8.48(d, 2H, J=5.0Hz).

(Received in Japan 9 July 1984)