SYNTHETIC STUDIES ON CARBAPENEM ANTIBIOTICS FROM PENICILLINS. V[1]. A STEREOSPECIFIC PREPARATION OF 4-ALLYLAZETIDINONES

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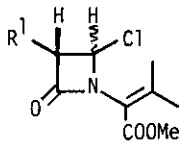
Abstract——— A stereospecific preparation of chiral 4-allylazetidinones 3, key intermediates for the synthesis of the carbapenem antibiotics, has been achieved in good yields by reaction of 4-acetoxyazetidinones 2 with allylsilanes in the presence of TMSOTf.

As part of our continuing program on ß-lactam antibiotics, we have investigated the synthesis of the optically active carbapenems by utilization of the penicillin ß-lactam as a chiral precursor.[2,3] In this investigation the regio- and stereospecific C-C bond formation at C-4 of the ß-lactam ring is one of the most dominant problems.[4] In the previous paper,[2] we reported a stereocontrolled allylation of the chiral 4-chloroazetidinone 1 with allylsilanes, which provided a means of preparing the key intermediates 3 for the synthesis of carbapenem antibiotics represented by thienamycins and carpetimycins.[3] In an effort to improve that allylation reaction, we have now found the more effective and operatively simpler reaction starting from 4-acetoxyazetidinones 2 as substrate. The reaction of 2 with the allylsilanes in the presence of trimethylsilyl triflate (TMSOTf) was stereospecific and gave high yields of the 4-allylazetidinones 3. We wish to report here this convenient allylation reaction of 2.

The starting material 2a for our initial examinations was prepared from the penicillin sulfoxide according to the method described in the literature.[5] Treatment of 2a (4R:4S = 2:1) with allyltrimethylsilane (2.5 equiv) in the presence of catalytic amount (0.1 equiv) of TMSOTf in dichloroethane at 90°C for 72 h



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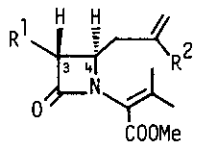

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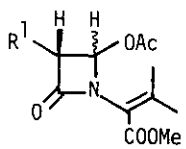

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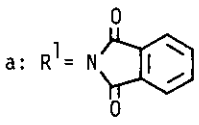
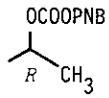


a: R^1 =



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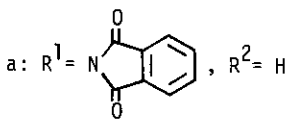

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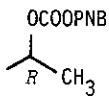
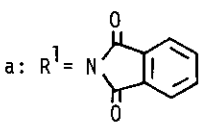
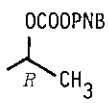


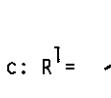
b: R^1 = , R^2 = H



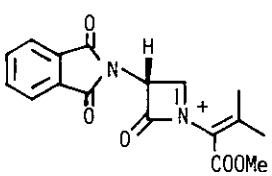
a: R^1 = (4R,S)



b: R^1 = (4R)



c: R^1 = , R^2 = $CH_2COOPNB$



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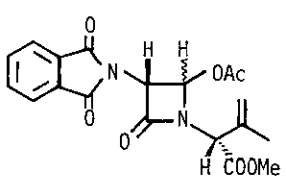

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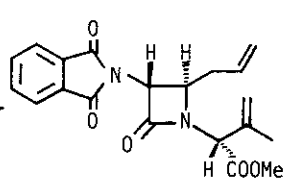

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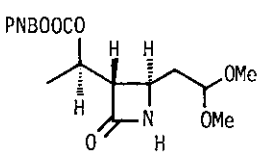

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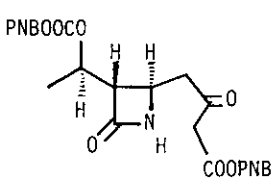

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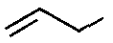
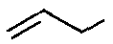
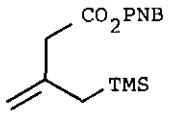
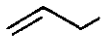
Table. Allylation Reaction of Acetoxyazetidinones

Entry	4-Acetoxy-azetidinone	Allylsilane	Reaction Conditions Temp. (°C)	Time (h)	Product	Yield (%)
1	2a		90	72	3a	76
2	2b		70	29	3b	73
3	2b		65	63	3c	82
4	5		75	29	6	74

afforded, after workup in the usual manner and purification by silica gel chromatography, 3,4-trans-4-allylazetidinone 3a in 76% yield (Table, Entry 1). The product 3 was identified by comparison with the sample prepared from 1a as described in the previous paper.[2] It is noteworthy that the reaction occurred stereospecifically and gave exclusively the trans product 3a in spite of the use of the 4R and 4S mixture as the starting 4-acetoxyazetidinone 2a. This result may imply that the reaction proceeded via the azetidinium ion 4, to which the allylsilane attacked stereoselectively from the less hindered ß-face of 4.

The present allylation method is generally applicable to other 4-acetoxyazetidinones. Some of the results are summarized in the table. The reactions of 2b[6] with allyltrimethylsilane and *p*-nitrobenzyl 3-(trimethylsilylmethyl)but-3-enolate[2] gave allylazetidinones 3b,c in satisfactory yields (Entry 2 and 3), respectively. These products could be converted to key intermediates 7 and 8 for the synthesis of the thienamycin series of compounds.[2] The ß,γ-unsaturated ester 5 (4R:4S=1:3)[5] also gave the corresponding allylazetidinone 6[7] (Entry 4), which was smoothly isomerized to 3a by treatment with Et_3N in CH_2Cl_2 in quantitative yield. The product 3a could be an intermediate for the syntheses of carpetimycins[3].

The mildness and the ease of the reaction promise to permit the use of a variety of 4-acetoxyazetidinones as substrate. The present method thus provides a simple and expedient strategy for the synthesis of carbapenem antibiotics.

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7. Physical data for 6: IR(CH_2Cl_2) 1765, 1740, 1725, 1390cm^{-1}; NMR($CDCl_3$) δ 1.97(3H, s), 2.2-3.1(2H, m), 3.85(3H, s), 4.40(1H, ddd, J=3, 4.5, 9Hz), 4.90(1H, s), 5.0-5.4(5H, m), 5.4-6.2(1H, m), 7.83(4H, brs)ppm.

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