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STEREO- AND REGIOSPECIFIC ALLYLATION OF 4-CHLOROAZETIDINONES WITH ALLYLSILANES. CONVERGENT SYNTHESIS OF A KEY INTERMEDIATE FOR (+)-THIENAMYCIN

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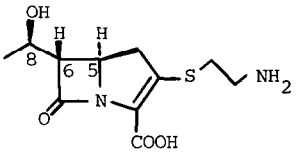
Summary An efficient stereospecific synthesis of optically active 4-allylazetidinones (6, 7, 11, and 15a,b) has been accomplished using silver-promoted coupling reaction of allylsilanes (5 and 14b) with 4-chloroazetidinones (3, 4, and 10a,b) derived from penicillins.

The potent, broad antibacterial activity and the unique chemical structure of the carbapenem family of antibiotics,[1] of which thienamycin (1) is a typical representative, have led to many recent efforts to synthesize these carbapenems in chiral form.[2,3] As part of our continuing program on β-lactam antibiotics, we are working to synthesize optically active carbapenems from penicillins (2) One of the most intriguing problems is to introduce, with correct stereocontrol, two properly functionalized alkyl groups into the C_5 and C_6 positions of 2 in place of its thio and amino groups. A noteworthy structural feature common to all of the carbapenems is the R configuration of C_5 unlike some variations at the C_6 position. Accordingly, we first focused our attention on introduction of the alkyl group into the C_5 position of 2.[4] We here report a stereospecific reaction of 4-chloroazetidinones (3, 4, and 10a,b) with allylsilanes (5 and 14b)[5] to produce the trans-substituted allylazetidinones (6, 7, 11, and 15a,b) and a short step synthesis of the key intermediates (16a,b) for (+)-thienamycin and 8-epithienamycin

If a planar azetidinium ion having a bulky substituent at the C_3 position (e.g. A) could be generated and subsequently trapped with certain nucleophiles, this would lead to the desired stereoselective trans-alkylation (Scheme 1). When the chloroazetidinone 3[6] was allowed to react with allyltrimethylsilane 5 in the presence of $AgBF_4$ in CH_2Cl_2 (-60-0°C, 2 h),[7] the trans-allylazetidinone 6 was obtained stereospecifically in 60-70% yields after silica gel chromatography and crystallization[8] The observed coupling constant ($J_{3,4}$ = 2.5 Hz) confirmed the 3,4-trans stereochemistry of 6. Examination of the crude product mixture revealed the absence of the corresponding cis-isomer. Similarly, reaction of the benzyl ester 4 with 5 afforded stereospecifically 7 in 50% yield.

In order to confirm the applicability of this reaction, the C_3 alkyl substituted chloroazetidinone 10b was coupled with 5. An epimeric mixture of the alcohols 8[9] was protected with *p*-nitrobenzyl chloroformate (*p*-dimethylaminopyridine, CH_2Cl_2, 0°C, 1 5 h) to give a mixture of the R- and S-carbonates 9a,b, separable by silica gel chromatography. Chlorination of the R-carbonate 9a (Cl_2, CH_2Cl_2-CCl_4, -78-0°C) led to an inseparable mixture of the C_4 epimeric chlorides 10a (cis : trans = 45 : 55) in 84% yield after silica gel chromatography. On the other hand, treatment of the S-isomer 9b with chlorine furnished a separable mixture of the two



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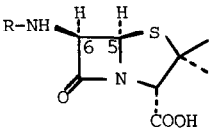

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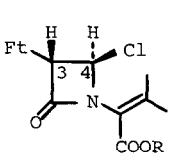
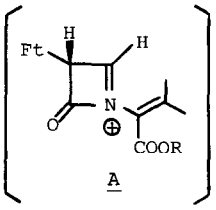
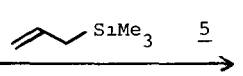


3 R = Me

4 R = Bzl



A



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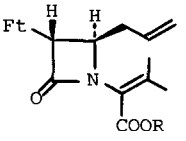
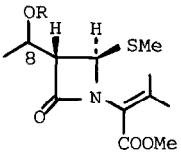


6 R = Me

7 R = Bzl



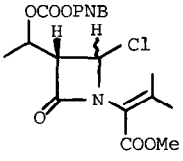
8 8RS, R = H

9a 8R, R = COOPNB

9b 8S, R = COOPNB

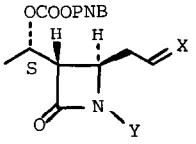
1 ClCOOPNB

2 Cl_2



10a 8R

10b 8S, cis

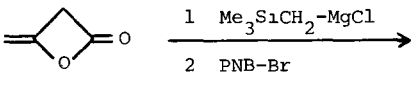


11 X = CH_2, Y = $C{=}CMe_2$ (COOMe)

12 X = O, Y = H

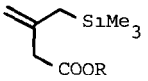
13 X = $(OMe)_2$, Y = H

SCHEME 1



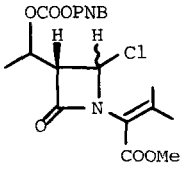
1 Me_3SiCH_2-MgCl

2 PNB-Br



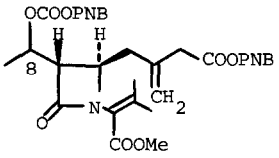
14a R = H

14b R = PNB



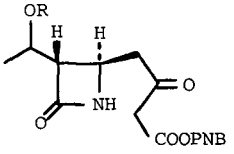
10a,b

14b



15a 8R

15b 8S



16a 8R, R = COOPNB

16b 8S, R = COOPNB

16c 8R, R = H

SCHEME 2

Ft = phthalimido, Bzl = benzyl, PNB = *p*-nitrobenzyl

C_4 epimers (cis trans = 65 35), from which, subsequent crystallization and silica gel chromatography gave the cis-chloride 10b (mp 154-157°C) and the trans-isomer (oil) in 46% and 25% yields, respectively. The coupling reaction of the cis-chloride 10b with 5 under the conditions described above afforded stereospecifically the allylazetidinone 11 in 78% yield. Ozonolysis (1 EtOAc, -78°C, 2 $NaHSO_3$ aq) followed by reductive methanolysis (Me_2S-MeOH-CH_2Cl_2, 0°C-RT, 4 h, 50°C, 6 h) provided the known aldehyde 12,[10] an intermediate for 8-epithienamycin, and its acetal 13 in 15% and 36% yields, respectively

Since the Merck group[3i] has shown that the azetidinone 16c, having a γ-substituted acetoacetate side chain at its C_4 position, is a versatile intermediate for synthesizing thienamycin, we have concentrated on the exploitation of a convergent synthetic method for this key intermediate (Scheme 2) We considered that such acetoacetates 16 could directly be prepared by reaction of 2-(alkoxycarbonylmethyl)allyltrimethylsilane 14, a regiospecific γ-anion equivalent of the acetoacetate, with 4-chloroazetidinones 10 and subsequent oxidative removal of the extra carbon atoms from the coupling products 15.[11] The requisite allylsilane PNB ester 14b can be readily prepared by esterification of 3-(trimethylsilylmethyl)but-3-enoic acid 14a (*p*-nitrobenzyl bromide, Et_3N, DMF, 0°C, 4 h 66%, bp 160°C/0.05 torr), which was synthesized by coupling of diketene with trimethylsilylmethylmagnesium chloride as described by Itoh et al [12] The silver-promoted reaction of the allylsilane 14b with the chloroazetidinones 10a,b proceeded stereo- and regiospecifically to give the allylazetidinones 15a,b in 58% and 69% yields, respectively Oxidative removal of the extra carbon atoms from 15a,b as above afforded the acetoacetates 16a,b in 73% and 78% yields, respectively The compound 16a was identified by comparing its spectra (ir and nmr) with those of (±)-16a which had already been converted to (±)-thienamycin [13]

Since this two-step conversion of the chloroazetidinones 10 to the carbapenem precursors 16 affords good yields under mild reaction conditions with tolerance of the various functional groups and demonstrates the allylsilane 14b to be a stable, easy-handling γ-anion equivalent of the acetoacetate, we believe that the present study provides a convergent synthetic method for (+)-thienamycin and other trans-substituted carbapenem antibiotics

The compound 6 could be deprotected to the amine (6 Ft = NH_2) in good yield Using this compound as a key intermediate, further work is in progress to develop an alternative synthetic method for preparing the carbapenem antibiotics

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4. At the onset of our study, the Shıonogı group[31] had reported that reactıon of the chloro-azetıdınone (3 Ft = TrNH, R = $CHPh_2$) wıth allylcuppers resulted ın the formatıon of the desıred allylazetıdınones The products, however, were 2 1 mıxtures of the C_4 stereoısomers

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8 After completıon of our work [M Hashımoto, M. Aratanı, and K. Sawada, European Patent 35689 (9 19, 1981)], several methods for alkylatıon at the C_4 posıtıon of azetıdınones have been reported (a) G.A. Kraus and K. Neuenschwander, J.C.S. Chem. Commun., 134 (1982), (b) P.J. Reıder, R Rayford, and E J.J Grabowskı, Tetrahedron Lett , 23, 379 (1982), (c) K. Prasad, P. Kneussel, G Schulz, and P. Stutz, ıbıd , 23, 1247 (1982), (d) T Kametanı, N. Kanaya, T Mochızukı, and T Honda, Heterocycles, 19, 1023 (1982), (e) C.W Greengrass and D W.T. Hoople, Tetrahedron Lett , 22, 5335 (1981), (f) C W Greengrass and M.S Nobbs, ıbıd., 22, 5339 (1981), (g) A G M. Barrett and P. Quayle, J.C S. Chem. Commun., 1076 (1981), (h) ref 3d and earlıer references cıted therein.

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11. Durıng our work was ın progress, several methods to ıntroduce acetoacetate equıvalents were reported (a) ref 3d, (b) ref 8b, (c) S Oıda, A Yoshıda, and E Ohkı, Chem. Pharm. Bull , 28, 3494 (1980), (d) T. Kametanı, T. Honda, A Nakayama, and K. Fukumoto, Heterocycles, 14, 1967 (1980), T. Kametanı, T Honda, A. Nakayama, Y. Sasakı, T Mochızukı, and K. Fukumoto, J C S Perkın Trans I, 2228 (1981).

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13. T Kametanı, S.-P. Haung, T Nagahara, S Yokohama, and M Ihara, J C S Perkın Trans I, 964 (1981)

14. Selected data, 6 mp 105-106°C, IR (CH_2Cl_2) 1770 (sh), 1760, 1720 cm^{-1}, ^1H NMR ($CDCl_3$) δ 2.12 (s, 3H), 2.26 (s, 3H), 2.52 (m, 2H), 3.83 (s, 3H), 4.42 (ddd, 1H, J = 2.5, 5, 7 Hz), 4 9-5.3 (m, 2H), 5.12 (d, 1H, J = 2 5 Hz), 5 5-6 0 (m, 1H), 7.82 (m, 4H) 15a IR (CH_2Cl_2) 1750, 1720 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.46 (d, 3H, J = 6 5 Hz), 1 95 (s, 3H), 2.19 (s, 3H), 2.50 (m, 2H), 3 06 (dd, 1H, J = 2.5, 7 Hz), 3 13 (s, 2H), 3.74 (s, 3H), 4.10 (ddd, 1H, J = 2.5, 6, 7 Hz), 5.01 (s, 2H), 5.17 (quıntet, 1H, J = 7 Hz), 5 20 (s, 2H), 5.25 (s, 2H), 7.48 (d, 2H, J = 9 Hz), 7 52 (d, 2H, J = 9 Hz), 8.18 (d, 4H, J = 9 Hz) 16a $[\alpha]_D^{22}$ +21 8°.

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