Tetrahedron Letters,Vol.26,No.7,pp 937-940, 1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

STEREOCONTROLLED TOTAL SYNTHESIS OF THE CHIRAL BUILDING BLOCK (3S,4R)-3-[(R)-1-HYDROXYETHYL]-4-ACETYLOXY-AZETIDIN-2-ONE: A USEFUL SYNTHON FOR THE SYNTHESIS OF (+)-THIENAMYCIN, CARBAPENEMS AND PENEMS&

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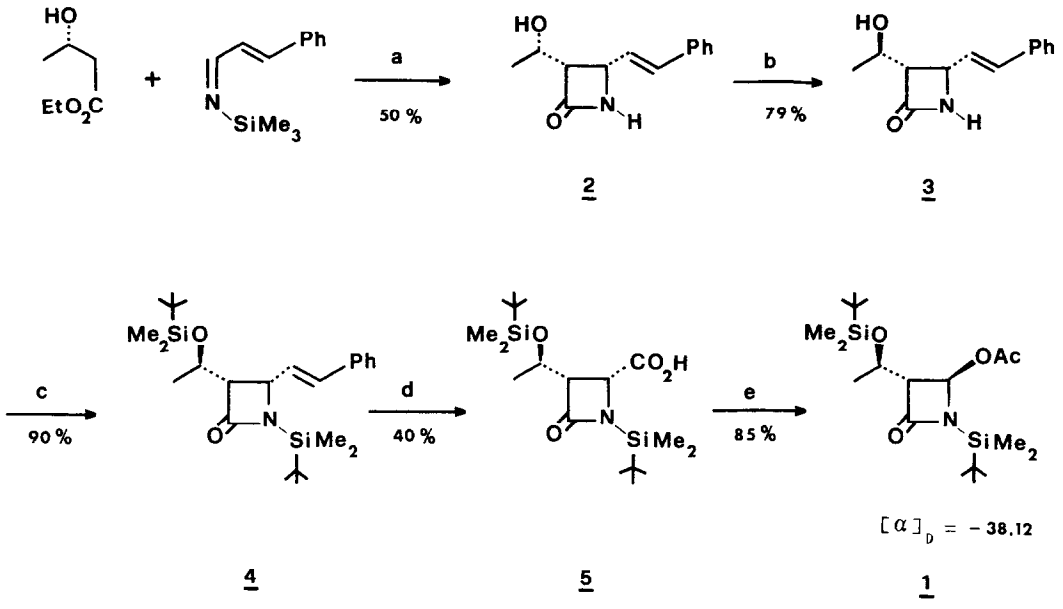
Abstract: A total stereocontrolled synthesis of (1), an intermediate in the synthesis of (+)-thienamycin, carbapenems and penems, based on a strategy that uses the S(-)hydroxy ethylbutyrate as chiral building block, is reported.

Carbapenems and penems are a new generation of β-lactam antibiotics which are endowed with unique structure and usually potent antibacterial activity. Synthetic efforts in this area have resulted in the total synthesis of a number of these substances.[1] Recently it has been shown by several research groups that the hydroxyethyl-azetidinone (1), which contains all chiral centers in the correct configuration, constitutes one of the best synthons for the preparation[2,17] of these antibiotics. We wish to report here a new, fully stereocontrolled synthesis of (1) in optically active form involving an electrophilic substitution by a trimethylsilylimine on a nucleophilic ester enolate.

Recently Hart et al.[3] have found that N-trimethylsilylimines react with ester enolates to give in one step the corresponding N-unsubstituted azetidinones. However, there is no successful report, to our knowledge, on the chiral synthesis of 3-hydroxy-ethyl-azetidinones following this approach.

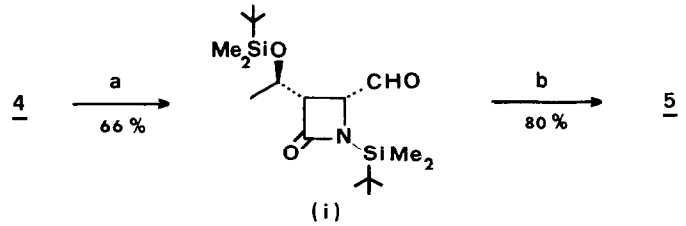
We have now found that the dianion obtained at -78°C from S-(-)hydroxyethyl butyrate with two equivalents of lithium bis(trimethylslyl)amide in tetrahydrofuran reacts at -78 to 20°C with one equivalent of N-trimethylsilylcinnamilydenimine[4] to give a 50% yield of a mixture of (3S,4S)- and (3S,4R)-3-/(S)-1-hydroxyethyl/-4-styryl azetidin-2-one (2) in a 70/30 ratio[5,6] (SCHEME I). No trace of the corresponding (3R)-isomers could be detected among the reaction products. By this way the original chiral center of the (S)-3-hydroxy ethyl-butyrate is used to induce in a lk-1,2 manner[7] the new chirality at the adiacent carbon C(3) during the formation of the C(5)-C(3) carbon bond. A similar lk-1,2 induction with 91%

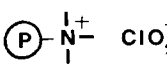
SCHEME I



a) lithium hexamethyl disilazide −78° then room temp. 12 hours ; b) HCO_2H, diazoethyl dicarboxylate, Ph_3P, OH^- ; c) t−butyldimethylsilylchloride, DMAP; d) RuO_2, $NaIO_4$, acetone, H_2O ; e) $Pb(OAc)_4$, $Cu(OAc)_2$, CH_3CN.

SCHEME II



a) O_3, CH_2Cl_2, Zn, AcOH ; b)  ClO_2^- , THF, AcOH.

selectivity has been also observed in the alkylation of the same ester enolate with methyl iodide[8]. In contrast a much lower stereoselectivity has been found in the formation of the C(4) center which leads to a 70/30 mixture of the 4S and 4R configuration.[9] This lack of stereocontrol is , however, unimportant since the C(4) center is equilibrated to the more stable 4R configuration in a later step of the synthesis. Inversion of the hydroxyl group on the side chain from S to R configuration was then achieved by treating the Z/E mixture of (2) with formic acid in the presence of triphenylphosphine and diethylazodicarboxylate.[10] Alkaline hydrolysis of the cleanly inverted formate esters provide the Z/E mixture of (3) in 79 % yield based on (2), no elimination product being detected in the reaction mixture. The yield of the inversion appears to be surprisingly high when compared with analogous results in olivanic acid derivatives with the same hydroxy ethyl side chain configuration[11] Cleavage of the styryl group to the corresponding acid (5) could be accomplished, previous conversion of the isomeric mixture into its bis-terbutyldimethylsilyl derivative (4) (N,N-dimethylamino-pyridine, CH_2Cl_2, ter-butyldimethylsilyl chloride), by means of sodium metaperiodate in aqueous acetone in the presence of ruthenium trichloride[12]. The mixture of the acids was processed without purification to give, as single product, the 4(R)-acetate (1) by treatment with lead tetracetate in acetonitrile and a catalytic amount of copper acetate[13]. This compound (1) was identical in all respects with an autentical sample obtained by an alternative synthesis[14].

An improved route to (5), starting from (4) (SCHEME II), involves a convenient oxidative cleavage of double bond recently developed from these laboratories.[15] Thus ozonization of (4) in methylene chloride at -78°C until deep blue solution, followed by reduction of ozonide with Zn in acetic acid, and oxidation of the crude aldehyde so obtained by a new polymer-bound chlorite reagent[16], furnished the previously reported compound (5) in 53% overall yield starting from (4). Since the conversion of the bis-protected compound (1) into thienamycin and carbapenems has already been described, this reaction sequence affords a formal synthesis of (+)-thienamycin[17, 18].

Acknowledgements: We are indebted with Prof. A. Bongini for helpful discussion on the ^{13}C NMR spectra and to Dr. Franceschi for generous supply of compound (1). This work has been supported by a grant from "Progetto Finalizzato Chimica Fine e Secondaria. C.N.R. Rome).

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&) Presented in part at Fifth International Conference On Organic Synthesis. Freiburg (RFT) August/1984

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5) The use of LDA instead of Li-hexamethyldisilazide doesn't result in changing of yield and ratio of E/Z isomers.

6) Yields are reported for isolated chromatographically pure products and have not been optimized. ^{1}H NMR, MS, IR spectra were enterely consistent with the assigned structures and satisfactory combustion analyses were obtained. Selected spectroscopic data of selected compounds as follow:
2: I.R. 3500, 3400, 1740;
60 MHz ^{1}H NMR ($CDCl_3$) 7.3 (5H Ar); 6.7 (d J=16Hz 1H); 6.6 (N-H); 6.3 (1H dd J=6Hz and 16Hz); 4.4(C_4H dd J=6 e J=7Hz 1H); 4.1 (C_5H q J=6Hz); 3.33 (dd J=6Hz e J=7Hz C_3H 1H); 2.8 (OH); 1.25 (3H d J=6Hz);
^{13}C NMR (Varian FT 80 MHz)($CDCl_3$) 170.0 C_2; 135.9; 128.7; 128.2; 126.6; C-Ar; 134.3 C_8; 125.6 C_7; 53.4 C_4; 61.5 C_5; 64.8 C_3; 21.8 C_6 ;
3; I.R. 3500, 3400, 1740;
^{13}C NMR 168.7 C=O; 135.8; 128.3; 127.6; 126.2 C-Ar; 132.5 C_8; 125.9 C_7; 63.6 C_4; 62.1 C_5; 52.8 C_3; 21.2 C_6;
1: IR 1750, 1740, 1250;
60 MHz ^{1}NMR ($CDCl_3$) 0.33, (12H m); 0.95 (18H m); 1.35 (3H d J=6Hz); 2.1 (3H s); 3.2 (1H broad d J=6Hz); 4.2 (1H quintet J=6Hz) 5.85 (1H broad s)
^{13}C NMR 170.0 C_2, 169.4 OC=O; 63.9 C_3; 76.2 C_4; 67.3 C_5; 21.0 C_6;

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16) This polymer-supported reagent was prepared by washing the chloride form of the Resin Amberlist A-26 (Rohm and Haas), with a dilute (8%) aqueous sodium chlorite solution. The content of the oxidizing species resulted to be 1.5 meq/g of wet resin (iodometric titration). The polymeric reagent so obtained was reacted with crude aldehyde (i) in acetic acid/THF 1/1 mixture, at room temperature for 1 hour. After evaporation of the solvent at reduced pressure the acid (5) was obtained in 80% yield (SCHEME II).

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(Received in UK 14 December 1984)