

SYNTHESIS OF (S)-N-(BENZYLOXY)-4-ACETOXYMETHYL-2-AZETIDINONE, POTENTIAL INTERMEDIATE FOR CARBAPENEM ANTIBIOTICS, BY CHEMOMICROBIOLOGICAL APPROACH

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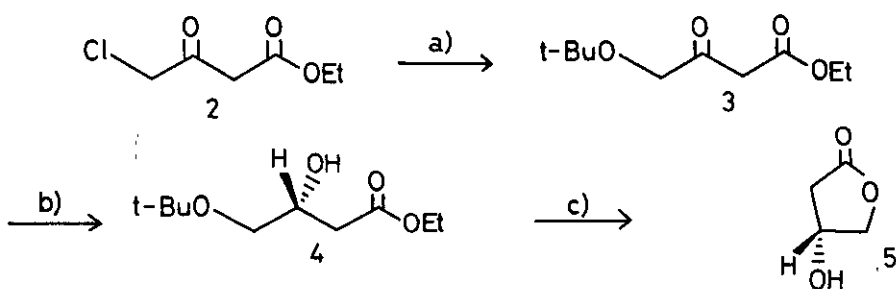
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Abstract- (R)-Ethyl 4-t-butoxy-3-hydroxybutanoate, which was prepared by baker's yeast reduction of ethyl 4-t-butoxy-3-oxobutanoate, was converted to (R)-3-hydroxybutyrolactone. After cleavage of the lactone ring with N-benzyloxyamine, β -lactam cyclization of the hydroxamate was carried out by Mitsunobu procedure with complete inversion of configuration at C-3 to give (S)-N-(benzyloxy)-4-acetoxymethyl-2-azetidinone. The corresponding (R)-azetidinone was also synthesized from natural (S)-malic acid via (S)-3-hydroxybutyrolactone.

The recent discoveries of thienamycin¹ and related carbapenem antibiotics have stimulated considerable interest in the development of general strategies for the enantioselective synthesis of these naturally occurring products². In these antibiotics, the (R)-configuration at C-5 in carbapenems is considered to be essential for antibiotic activity³. Therefore, the synthesis of chiral 4-substituted 2-azetidinones having the proper configuration at C-4 in azetidinones is still required⁴.

Our strategy for the synthesis of the 2-azetidinone was based on the use of chiral building block prepared by microbial reduction. The use of baker's yeast (*Saccharomyces cerevisiae*) as a chiral reducing reagent is of particular advantage because it is a cheap and easily available. Condensation of chiral 3-hydroxybutanoates prepared by biochemical methods⁵ and imines has been recently applied to the synthesis of the carbapenem antibiotics⁶. In order to synthesize the 2-azetidinone derivative **1**, it is necessary to obtain chiral 4-alkoxy-3-hydroxyesters. This is due to the fact that two terminal carbons have different

oxidation states and two hydroxy groups have different types of protection. As a result of the structural features, the carbapenem skeleton will be elaborated at the terminal carbon and carbapenem side-chain will be introduced at C-3 in azetidinones. Seebach reported that the 4-alkoxy-3-ketoesters are good substrates for fermenting baker's yeast reduction⁷. We also found that the yeast reduction of the 4-alkoxy-3-ketoesters provides efficient access to the chiral synthon⁸. We describe here preliminary results of a study, outlining a chemomicrobiological method to synthesize (S)-N-(benzyloxy)-4-acetoxymethyl-2-azetidinone 1. The substrate 3 for the reduction of *S. cerevisiae* was prepared by treatment of ethyl 4-chloroacetoacetate 2 with sodium hydride and t-butanol in 69% yield.



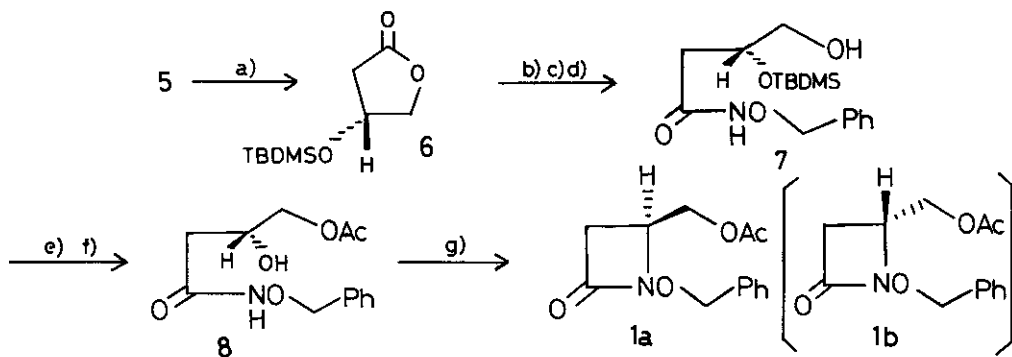
a) NaH, t-BuOH, THF b) *S. cerevisiae* c) trifluoroacetic acid

Fig-1

The reduction of the 3-ketoester 3 was carried out as follows. Dry baker's yeast (15 g) (*S. cerevisiae*; Oriental Yeast Co.) was dispersed in 500ml of tap water at room temperature for 0.5 h. To this suspension was added 1.0 g of 3 and the mixture was stirred for 20 h. After centrifugation at 12,000xG, the reaction mixture was extracted with ethyl acetate and purified by silica gel column chromatography to give (R)-4-t-butoxy-3-hydroxybutanoate 4 (0.638 g, 62%). The 3-hydroxy ester 4 was subjected to lactonization with trifluoroacetic acid at -5°C to give (R)-3-hydroxybutyrolactone 5 in 58% yield⁹. The absolute configuration of the lactone 5 was established by comparing its $[\alpha]_D$ value [+75.9° (c=1.469, CHCl₃)] with that of literature^{7,10}. The authentic samples were also prepared from (R)- and (S)-malic acid, respectively¹¹. The optical purity of the lactone 5 was determined by ¹H-nmr spectroscopy of the corresponding (-)-MTPA ester¹² and found to be 91.5%ee.

The construction of β-lactam ring required complete inversion of configuration at C-3 in 8. We applied the method developed by Miller¹³ to the formation of the β-

lactam ring. Protection of 5 with TBDMSCl afforded the protected lactone 6 in 86% yield. Direct conversion of 6 into the hydroxamate 7 with benzyloxyamine was failed, but we realized the transformation via three-step process. Cleavage of the lactone 6 with hydrazine monohydrate in ethanol gave rise to the hydrazide, which upon treatment with sodium nitrite in water containing 1.2 N hydrochloric acid at -5°C followed by treatment of the resultant azide with benzyloxyamine in ether afforded the hydroxamate 7 in 72% overall yield.



a) TBDMSCl, Imd., DMF b) H_2NNH_2 , EtOH c) NaNO_2 , 1.2N HCl, d) $\text{H}_2\text{NOCH}_2\text{Ph}$, Et_2O
 e) Ac_2O , Py., CH_2Cl_2 f) $n\text{-Bu}_4\text{NF}$, THF g) PPh_3 , $(\text{EtO}_2\text{CN})_2$

Fig-2

Protection of the hydroxy group in 7 with acetic anhydride (96%) followed by cleavage of *t*-butyldimethylsilyl group with tetrabutylammonium fluoride gave the 3-hydroxyhydroxamate 8 in 88% yield. The cyclization of 8 with triphenylphosphine, diethyl azodicarboxylate^{13,14} in THF gave (*S*)-*N*-(benzyloxy)-4-acetoxymethyl-2-azetidinone¹⁵ 1a in 77% yield. Above procedure was adopted to synthesize the corresponding (*R*)-azetidinone¹⁶ 1b from natural (*S*)-malic acid.

In summary, we established the chemomicrobiological approach to the chiral 4-substituted 2-azetidinone. It is important to note that the yeast reduction of 4-alkoxy-3-oxobutanoates provides a useful chiral building block which is formally derived from expensive (*R*)-malic acid.

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 16. $[\alpha]_D$ value of the (R)-azetidinone 1b is -11.37° (c=0.935, CHCl₃).

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