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

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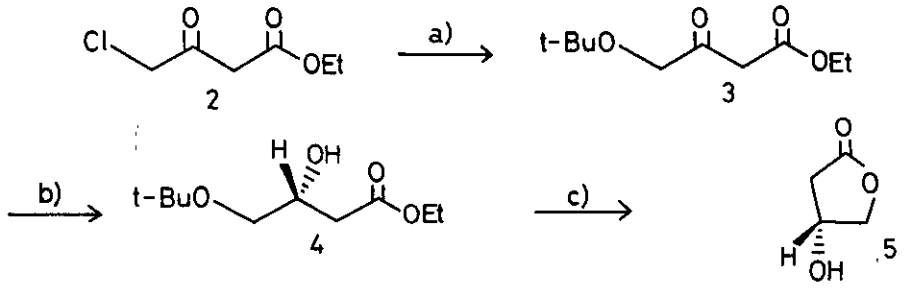
Abstract- (R)-Ethyl 4-t-butoxy-3-hydroxybutanoate, which was prepared by baker's yeast reduction of ethyl 4-t-butoxy-3-oxobutanoate, was converted to (R)-3-hydroxybutyrolactone. After cleavage of the lactone ring with N-benzyloxyamine, β-lactam cyclization of the hydroxamate was carried out by Mitsunobu 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 thienamycin[1] and related carbapenem antibiotics have stimulated considerable interest in the development of general strategies for the enantioselective synthesis of these naturally occurring products[2]. In these antibiotics, the (R)-configuration at C-5 in carbapenems is considered to be essential for antibiotic activity[3]. Therefore, the synthesis of chiral 4-substituted 2-azetidinones having the proper configuration at C-4 in azetidinones is still required[4].

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 methods[5] and imines has been recently applied to the synthesis of the carbapenem antibiotics[6]. 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 reduction[7]. We also found that the yeast reduction of the 4-alkoxy-3-ketoesters provides efficient access to the chiral synthon[8]. 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.



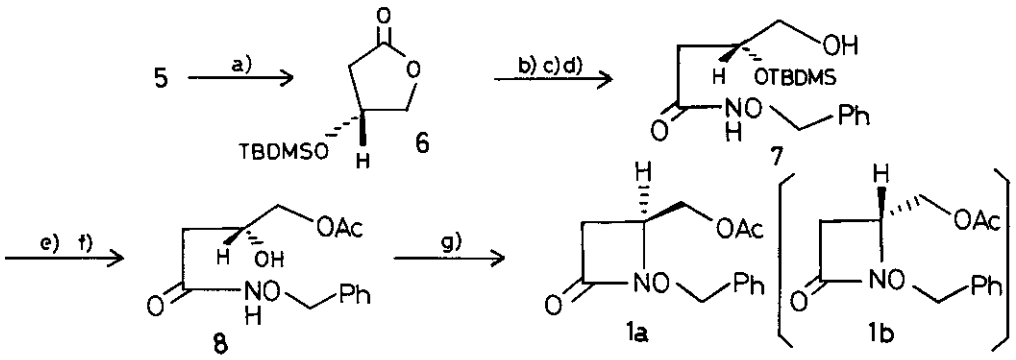
a) NaH, t-BuOH, THF b) S. cerevisiae c) trifluoroacetic acid

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% yield[9]. The absolute configuration of the lactone **5** was established by comparing its $[\alpha]_D$ value [+75.9°(c=1.469, $CHCl_3$)] with that of literature[7,10]. The authentic samples were also prepared from (R)- and (S)-malic acid, respectively[11]. The optical purity of the lactone **5** was determined by ^{1}H-nmr spectroscopy of the corresponding (-)-MTPA ester[12] 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 Miller[13] 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) H_2NOCH_2Ph, Et_2O
e) Ac_2O, Py., CH_2Cl_2 f) n-Bu_4NF, THF g) PPh_3, $(EtO_2CN)_2$

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-azetidinone[15] 1a in 77% yield. Above procedure was adopted to synthesize the corresponding (R)-azetidinone[16] 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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15. $[\alpha]_D$ +12.05°(c=0.838, $CHCl_3$); ir (neat, cm^{-1}) 1770, 1740, 1370, 1210, 1050; ^1H nmr ($CDCl_3$, δ) 2.07(3H, s, $COCH_3$), 2,52(1H, dd, J=14.0, 2.6 Hz, C-3H), 2.74(1H, dd, J=14.0, 5.5 Hz, C-3H), 3.68-3.74(1H, m, C-4H), 4.02(1H, dd, J=12.2, 4.3 Hz, CHOAc), 4.18(1H, dd, J=12.2, 3.8 Hz, CHOAc), 4.93(1H, d, J=11.3Hz, CH_2Ph), 4.97(1H, d, J=11.3 Hz, CH_2Ph), 7.30-7.41(5H, m, Ph); ms (m/z) 250(M^++1, 23.9%), 249(M^+, 22.7%), 208(M^+-42, 1.1%).

16. $[\alpha]_D$ value of the (R)-azetidinone **1b** is -11.37°(c=0.935, $CHCl_3$).

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