SYNTHESIS OF 3-HYDROXYETHYL-4-OXOAZETIDIN-2-YLPHOSPHONATE DERIVATIVES: POTENTIAL PRECURSORS TO CARBAPENEM AND α-AMINOPHOSPHONIC ACID DERIVATIVES

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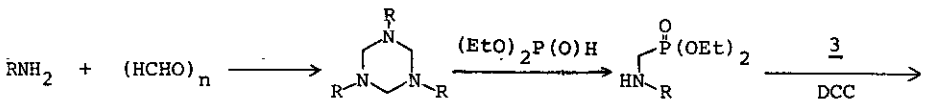
Abstract - Optically active 3-hydroxyethyl-4-oxoazetidin-2-ylphosphonate derivatives were synthesized.

4-Oxoazetidin-2-ylphosphonate derivatives, which should be potential precursors to the carbapenems, obtained from treatment of the corresponding 4-acetoxyazetidin-2-one derivatives with trialkyl phosphites have already been reported by Campbell[1] as the starting material of alanyl dipeptide containing organophosphorous moiety via β-phosphono-β-alanine derivatives. Such organophosphorous-containing molecules as the α-aminophosphonic acid dipeptide (for example: alaphosphine - an inhibitor of alanine racemase) are becoming increasingly important for pharmaceutical use. In this paper we wish to describe a new synthetic procedure for 4-oxoazetidin-2-ylphosphonate derivative by the ring closure of 2-bromo-3-hydroxybutyramides via the corresponding 2,3-epoxybutyramides which possess an activated methylene adjoining the amide nitrogen.

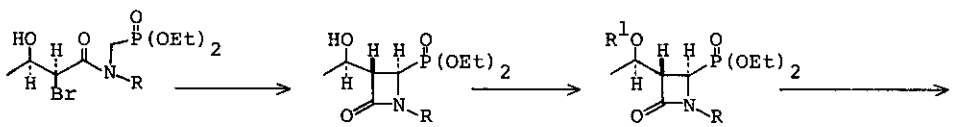
The starting phosphorous-containing butyramides were synthesized as follows: Treatment of anisidine or p-methoxybenzylamine with paraformaldehyde according to the procedure reported by Ratcliffe et al.[2] gave hexahydrotriazines, 1a (72%; mp 128-130° C) or 1b (95%; mp 113-115°C). Reaction of the hexahydrotriazines (1a and 1b) with diethyl phosphite at 100°C for 4-6 h gave secondery amines (2a, 61% and 2b, 65%). Amide formation reaction of the amines (2a and 2b) with 1 eq of (2S,3R)-2-bromo-3-hydroxybutyric acid (3)[3] in THF in the presence of 1 eq of DCC gave 4a (21%) and 4b (77%).

Next, these phosphorous-containing butyramides were cyclized to β-lactams in a stereospecific manner.[4] Treatment of 4a and 4b with 1 eq of lithium hexamethyldisilazide in THF at ice-cooling temperature for 5 min, and then another 1 eq of $LiN(SiMe_3)_2$ at 24°C gave chiral diethyl 3-hydroxyethyl-4-oxoazetidin-2-ylphosphonate derivatives, 5a (61%) and 5b (37%), and cis-isomers were not isolated. Protection of the hydroxy group of 5a with p-nitrobenzylchloroformate by use of 4-dimethylamino-

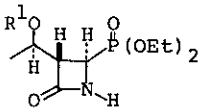
pyridine as a base in CH_2Cl_2 gave 6a (79%) as a foam. Deprotection of the methoxyphenyl group of 6a with 3 eq of cerium (IV) ammonium nitrite (CAN) in acetone-H_2O (3:2) gave 7A (81%) as a crystalline solid; mp 74-76°C. Hydrogenolysis of 7A with 5% Pd-C/H_2 at room temperature gave 7C (92%); mp 70-71°C; $[\alpha]_D^{24}$ -4.9° (c=0.59, $CHCl_3$). Similarly, protection of the hydroxy group of 5b with t-butyldimethylsilyl chloride by use of 4-dimethylaminopyridine as a base in DMF gave 6b (67%). Deprotection of the methoxybenzyl group of 6b with $K_2S_2O_8$-K_2HPO_4 in MeCN-H_2O (1:1) at 70-75°C under argon for 30 min gave N-free β-lactam 7B (57%) as a gum. These compounds (5a,b, 6a,b and 7A,B,C) should be potential precursors to new carbapenems and α-aminophosphonic acid analogues of aspartic acid.



a: R=p-Methoxyphenyl 1a 2a
b: R=p-Methoxybenzyl 1b 2b



4a, 4b 5a, 5b 6a, R^1=p-Nitrobenzyloxycarbonyl; 6b, R^1=t-Butyldimethylsilyl



7A, R^1=p-Nitrobenzyloxycarbonyl
7B, R^1=t-Butyldimethylsilyl
7C, R^1=H

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