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A convenient one-pot synthesis of 2β-(*O*-dibenzyl-phosphate)-oxymethyl-2α-methyl penam 3α-carboxylic acid benzyl ester and 3β-(*O*-dibenzyl-phosphate)-3α-methyl cepham 4α-carboxylic acid benzyl ester ☆

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Abstract—The 2β-(*O*-dibenzyl-phosphate)-oxymethyl-2α-methyl penam 3α-carboxylic acid benzyl ester and 3β-(*O*-dibenzyl-phosphate)-3α-methyl cepham 4α-carboxylic acid benzyl ester were synthesized. The conversion of the acyclic azetidione disulfides **1a–c** prepared by Kamiya's procedure to their bicyclic penam **2a–c** and cefam **3a–c** derivatives are described.

Interest in the biological activity of four coordinated tetrahedral phosphorous derivatives has grown tremendously in recent years. Anionic phosphonic acid monoester and monoamides have been shown to act as specific inhibitors of serine-β-lactamases,[1] either by acting as phosphorylating agents or as transition state analogs. The rationale behind the use of these compounds as inhibitors of serine-β-lactamases is that the four tetrahedral phosphorous in phosphonates, phosphonamidates as well in phosphates is a structural mimic of the putative tetrahedral intermediate that is formed during the serine-β-lactamase catalytic cleavage of β-lactam bond of bicyclic β-lactam substrates (penicillins and cephalosporins). Using this design principle, we have synthesized a series of penam and cepham containing triphosphate esters designed specifically to mimic the geometry of a Zn(II)-β-lactamase substrate at the transition state analog of tetrahedral intermediate.

A common feature to all metallo-β-lactamases investigated so far concerns the presence of two distinct Zn(II) ion binding sites. In the enzyme CcrA from *Bacteroides fragilis*, IMP-1 from *Pseudomonas aeruginosa*, and the binuclear form of BcII from *Bacillus cereus* one of the Zn(II) ions is coordinated by three histidine residues (Zn1 site); the second Zn(II) ion is ligated by aspartic, cysteine, and histidine residues as well as a water molecule. In addition a second water molecule is shared by both Zn(II) ions (presumably as a bridging hydroxide ion). This bridging hydroxide ion appears to serve as the nucleophile in the cleavage of the β-lactam bond of penicillin, cephalosporin as well as carbapenam antibiotics. In the structure of the mononuclear form of the BcII enzyme, the Zn(II) ion resides in the His site, tetrahedrally coordinated by its three histidine residues, and the nucleophilic hydroxide ion.[2] Thus we have explored the possibility of using a bicyclic β-lactam scaffold that contain a four coordinated tetrahedral phosphate triester with a good leaving group (benzyl ester group) that might act as a 'transition state analogue' inhibitor.

The molecules of interest in this study were 2β-(*O*-dibenzyl-phosphate)-oxymethyl-2α-methyl penam 3α-carboxylic acid benzyl ester and 3β-(*O*-dibenzyl-phosphate)-3α-methyl cepham 4α-carboxylic acid benzyl ester derivatives as potential inhibitors of mono- and binuclear-Zn(II)-β-lactamases. Therefore, the synthesis of a limited series of these penam and cepham triesters with variation in the substituents at the position 6 or 7, respectively, was undertaken. We believed that these

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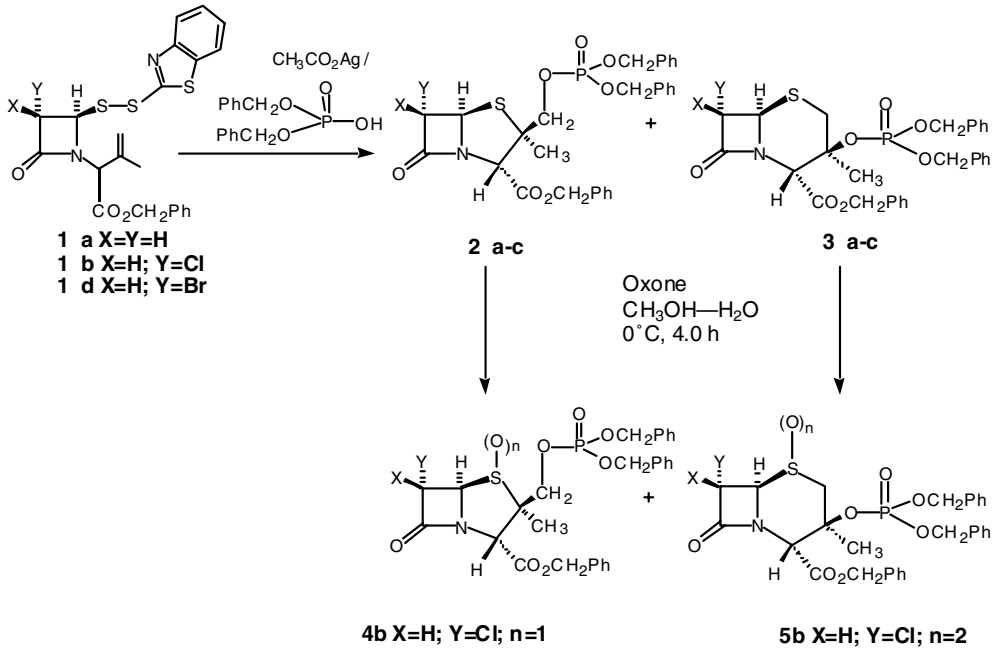

phosphate triesters present a structure and shape that mimics the high energy intermediate in phosphoryl transfer reactions.

The preparation of 2β-(*O*-dibenzyl-phosphate)-oxymethyl-2α-methyl penam 3α-carboxylic acid benzyl ester derivatives (**2a**–**c**) utilizing di-*O*-benzyl phosphoryl chloride requires the preparation of benzyl 2β-hydroxypenicillanate in a multistep synthesis. Unfortunately the alcohol proved to be unstable as was demonstrated by Baldwin et al.[3] due to the formation of a β-lactone due to the proximity of the β-oriented hydroxyl group to the β-lactam carbonyl group.

Based on this success, we report here a one-pot synthetic procedure allowing preparation of the derivatives (**2a**–**c** and **3a**–**c**, respectively) in reasonable preparative yields, starting from the disulfides (**1a**–**c**), prepared by Kamiya's procedure,[4] and treated with silver salt of acetic acid in the presence of a large excess of *O*-dibenzyl phosphoric acid in anhydrous CH_2Cl_2. The oxidation of the penam (**2b**) and cepham (**3b**) with oxone in CH_3OH–H_2O at 0 °C, gave the corresponding β-sulfoxide[5] of penam (**4b**), and the sulfone of cepham (**5b**) derivatives. The results are summarized in the following scheme.

Conclusion

In conclusion, we have prepared by one-pot reaction 2β-(*O*-dibenzyl-phosphate)-oxymethyl-2α-methyl penam 3α-carboxylic acid benzyl ester and 3β-(*O*-dibenzyl-phosphate)-3α-methyl cepham 4α-carboxylic acid benzyl ester. This approach allows for more greater control over the reaction through the use of benzyl 2β-hydroxy methyl-penicillanate, since it is well known that the 2β–hydroxymethyl penicillanate benzyl ester suffer from low chemical stability. The compounds **2a**–**c**, **4b**, **3a**–**c**, and **5b** generally appear to have the most promising characteristics since they are stable for several months.

It is noteworthy that for this class of functionalized 2β-*O*-phosphate-penam and 3β-*O*-phosphate-3α-methyl cepham derivatives this work represents the first example of the reaction of a disulfide such as **1a**–**c** treated *O*-dibenzyl phosphoric acid in the presence of silver salt of acetic acid. One of the important features of this approach is that this stereospecific reaction can be extended to introduce other phosphoric acid diesters as leaving groups.

We are presently investigating the application of the compounds synthesized as IMP-1 Zn(II)-β-lactamase inhibitors.

Supplementary information available: Experimental procedures and the ^1H NMR and ^{13}C NMR data for compounds **1a**–**c**, **2a**–**c**, **3a**–**c**, **4b**, and **5b** is available online with the paper in ScienceDirect.

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