A NOVEL PREPARATION OF 4-UNSUBSTITUTED β-LACTAMS

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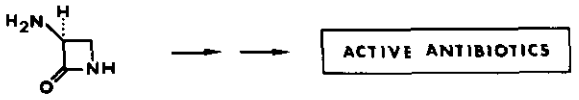
Abstract - The key intermediate (1) for monobactam synthesis has been prepared from 6-aminopenicillanic acid (6-APA) without using Raney nickel. Desulfurisation was accomplished by a two step process, involving a novel reduction reaction.

Until a few years ago, chemists believed that the antibacterial activity of β-lactam compounds was always associated with molecules possessing a second fused ring, and thus industrial research was essentially limited to the bicyclic systems.

This prejudice, however, was gradually allayed when researchers at the Fujisawa laboratories isolated the first monocyclic member in the family of biologically active β-lactams, i.e. the nocardicins[1] and recently, when investigators at the Squibb Institute and independently at the Takeda laboratories discovered the monobactams[2]. Although the isolated natural compounds exhibited only a low order of activity, chemical modification brought to light their unexpected potential and some of these novel monocyclic derivatives were indeed excellent antibacterials[3].

We wish to report here an efficient synthesis[4] of a key intermediate for monobactam production, namely (S)-3-aminoazetidin-2-one (1) from 6-aminopenicillanic acid (6-APA).

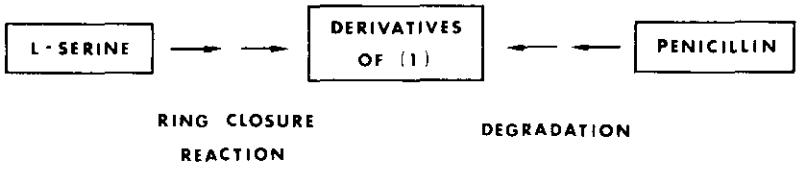


(1)

(1) has already been successfully converted to potent broad spectrum antibacterials by acylation of the amino group followed by sulfonation or various reactions with organic phosphorous compounds of the azetidinone-NH-group[3].

(S)-3-Aminoazetidin-2-one (1) and its acylated derivatives have been prepared[5] in moderate overall yield by ring closure reactions of L-serine derivatives.

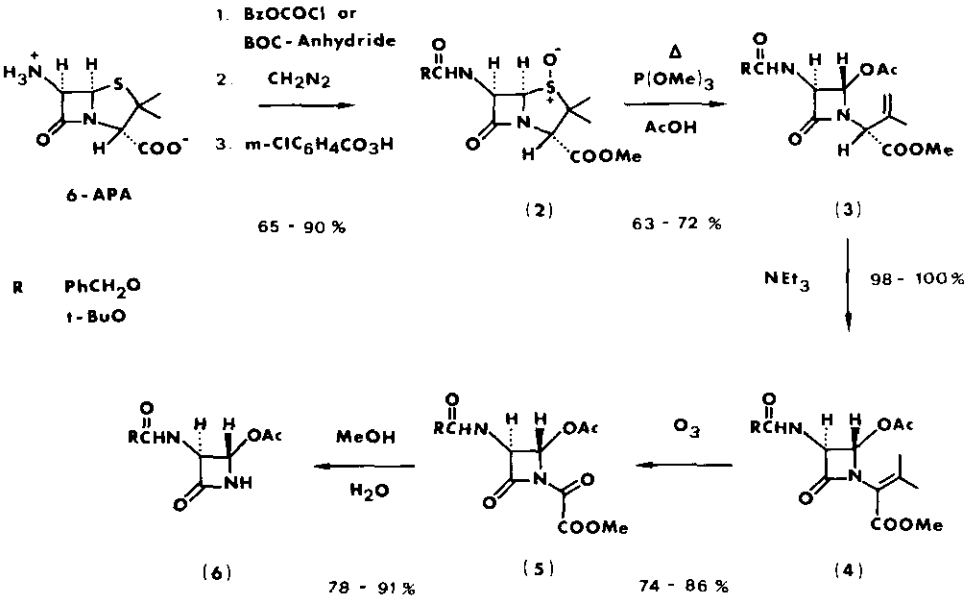
Alternatively, acylated derivatives of (1) have also been made[6,7] from penicillins or 6-APA by reductive desulfurisation using Raney nickel. These procedures[7] require an enormous excess of active metal, however.



As already mentioned, the starting material for our preparation of (1) is 6-APA, an inexpensive and readily available compound. We preferred the degradative approach because of our experience, that azetidinone syntheses by ring closure reactions are often very difficult to accomplish. A central point in our synthesis planning was the question: How can we remove the sulfur of 6-APA without using Raney nickel?

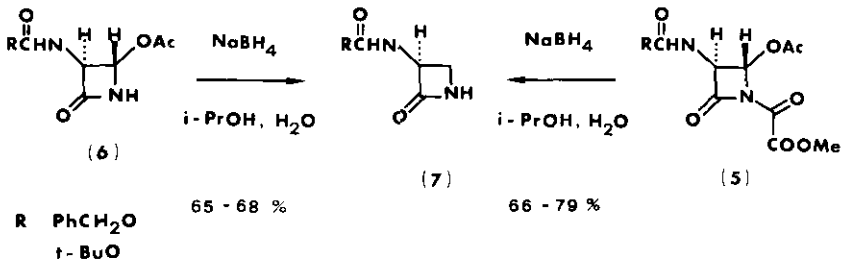
In the final version of our preparation of (1), the sulfur atom inherent in the penicillin was substituted by a hydrogen during a two step process.

Lombardi et al.[8] have already reported the ring opening reaction with penicillin sulfoxide esters to monocyclic acetoxy derivatives using trimethyl phosphite and acetic acid. Subsequent degradation led to 4-acetoxyazetidinones. This procedure represents the first step of the sulfur removal. In our hands it was most satisfactory with the benzyloxycarbonyl or the *tert*-butyloxycarbonyl protection groups; the low reactivity of the carbamate function not allowing the side chain to enter into undesired reactions commonly observed[9] with simple amide protection groups.



The resulting compound (6) now contains the main structural features of our (protected) target molecule (1) but also an additional acetoxy group. Although the replacement of acetoxy by hydrogen was by no means a general re-

action, this process representing the second and complementary step of sulfur removal, occurred easily with (6) and sodium borohydride at 0°C.



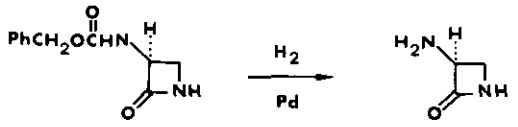
(6) (7) (5)

R PhCH$_2$O
t-BuO

65 - 68 % 66 - 79 %

A more convenient way to produce (7) was the direct treatment of (5) with sodium borohydride in aqueous solutions, involving oxamide hydrolysis and reduction of the acetoxy residue.

Finally the carbobenzoxy derivative (7a) (R = PhCH$_2$O) was hydrogenated over Pd on charcoal to yield target molecule (1), mp 77-83°C. On the other hand, selective deprotection of the BOC-protected compound (7b) (R = ^{t}BuO) using trifluoroacetic acid was unsuccessful. The BOC group has been found[3] to be a possible protection for some N-sulfonated β-lactam derivatives, however.

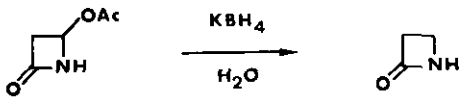


(7a) 100 % (1)

Along the whole reaction sequence the natural configuration of 6-APA was completely retained. Thus, an essential requirement in the production of monobactam antibiotics was met. The melting point and optical rotation of

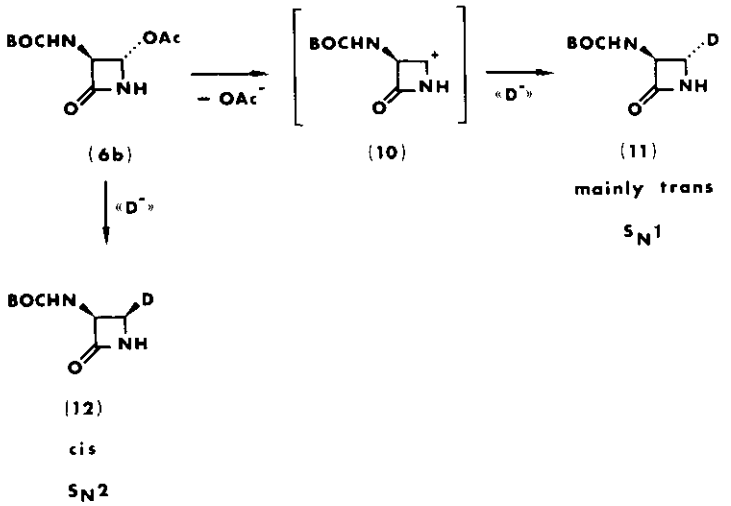
(7a) (164-165°C, -18±1° (c 1, MeOH)) were in full agreement with those determined with the product of the Raney nickel process (163-164°C, -17.8° (c 0.72, MeOH))[6].

To determine the scope of the novel reduction reaction, we have also prepared the simplest β-lactam (9), a compound extremely difficult to prepare[10] and therefore a touchstone in β-lactam synthesis. When 4-acetoxyazetidinone (8)[11] was reduced with 1.5 molar equivalents of potassium borohydride in water, (9) was produced. After vacuum distillation or crystallisation from ether-pentane, pure β-propiolactam (9), mp 73-74°C, was obtained.



(8) (9)

A remaining question was concerned with the stereochemistry of the reduction process: Would the *nucleophilic hydride species enter into* the β-lactam ring from the side of the acetoxy leaving group or would it attack from the opposite face?



(6b) (10) (11) mainly trans S_N1

(12) cis S_N2

An experiment using the (3S,4S)-4-acetoxy-3-*tert*-butyloxycarbonylaminoazetidin-2-one (6b) (R = ^{t}BuO) and sodium borodeuteride revealed, according to NMR (Fig. 1), that the deuterium was mainly incorporated with retention of configuration, forming the trans product (11) predominantly, a finding consistent with the monomolecular S_N1 mechanism and the intermediate formation of a carbonium ion (10). The preference for (11) over (12) arises upon steric control by the adjacent asymmetric C-3-carbon atom.

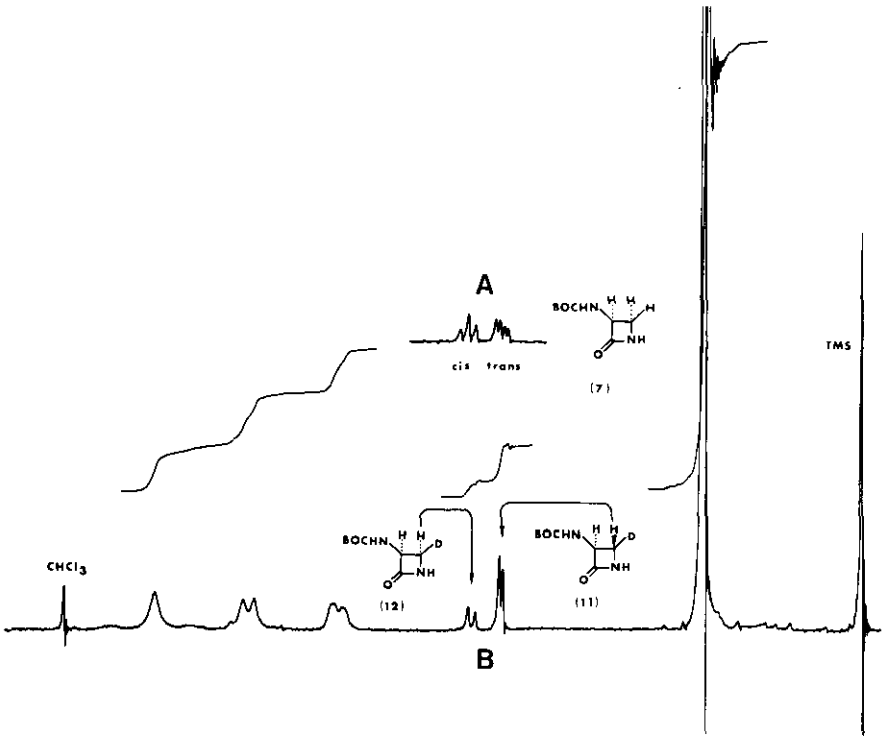


Fig. 1 NMR-spectra (80 MHz) of reaction products of (6b) with sodium borohydride (A) and sodium borodeuteride (B).

A similar reactivity has also been observed[11] in the substitution reactions of 4-acetoxyazetidin-2-ones with sulfur nucleophiles. For the borohydride ion, with regard to its bimolecular reactions towards many alkyl halides and alkyl sulfonates, the observed monomolecular mechanism might seem uncommon at the first sight. However, Brown et al. had already shown[12] in 1962, that car-

bonium ion trapping with sodium borohydride is also possible and in this mechanistic view the reduction of 4-acetoxyazetidin-2-ones can be regarded as an novel application of a long known principle.

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