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Preparation of Des-3-Hydroxy-Picolinoyl Pristinamycins I

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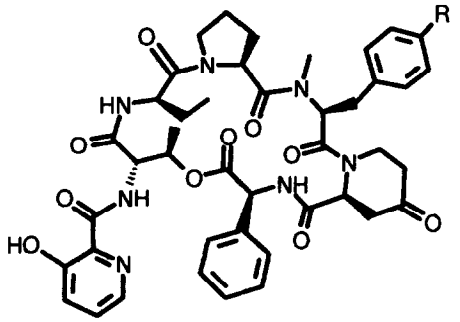
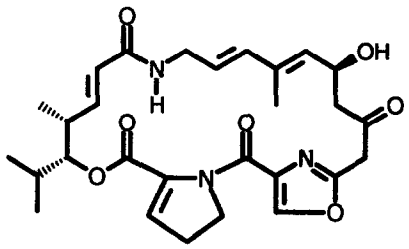
Abstract : The cleavage of the 3-hydroxy-picolinoyl residue of pristinamycin I_A and related compounds is reported to occur by a simple zinc reduction in aqueous acidic solution.

Pristinamycin is a naturally occurring antibiotic streptogramin, made up of two groups of molecules - pristinamycins I and pristinamycins II- which act synergistically on sensitive strains[1]. We recently reported our studies in the streptogramin field which have culminated in the selection for clinical trials of two new water-soluble derivatives of pristinamycin I and II (RP 59500; Synercid®)[2]. Pristinamycins I, among which pristinamycin I_A and I_B are the major components, are peptidic macrolactones whereas pristinamycins II are polyunsaturated macrolactones (**Figure 1**).



R = NMe_2 pristinamycin I_A (1)
R = NHMe pristinamycin I_B (2)
R = H virginiamycin (3)

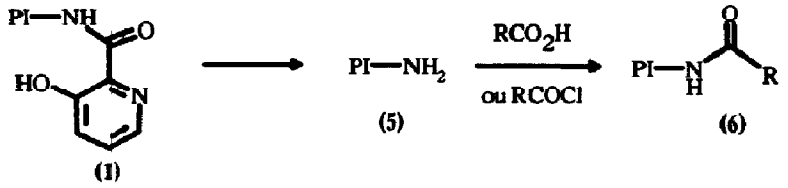


pristinamycin II_A (4)

Figure 1

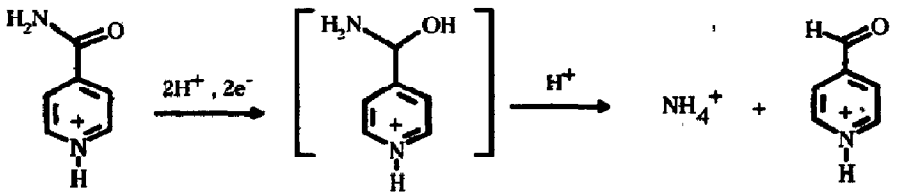
In our continuing exploration of the structure-activity relationships within the pristinamycin I (PI) series, we were particularly interested in the cleavage of the amide bond of the 3-hydroxy picolinoyl residue. This amide which is the only exocyclic amide of the molecule, has indeed been regarded for years as a necessary feature for the bacteriological activity of PI[3]. Therefore, we wondered whether the preparation of des-3-

hydroxy-picolinoyl PI (5) followed by the condensation of the resulting amine with various acids, according to a strategy reminiscent of that used so successfully in the penicillin area[4], could lead to new antibiotics (6) :



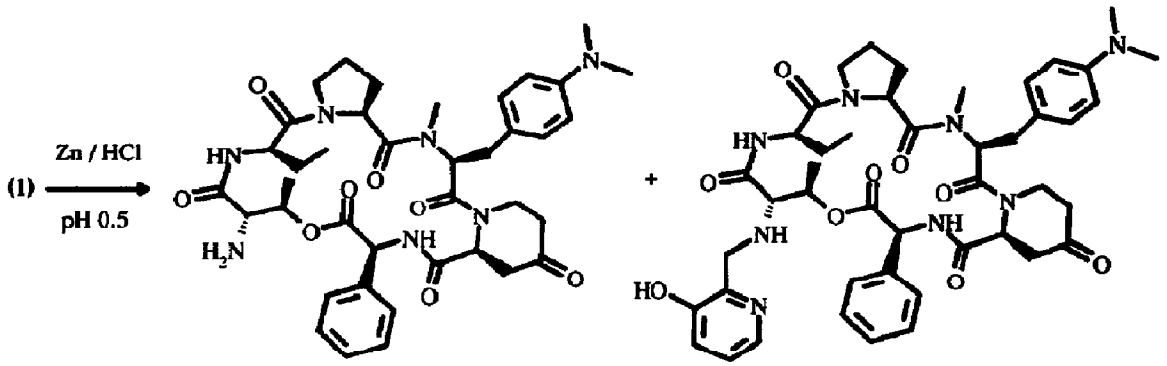
However, at the onset of this work, we were fully aware of the problems associated with this cleavage. On the one hand, we had to distinguish the picolinamide from five other amide bonds without jeopardising the sensitive lactone and carbonyl functions. On the other hand, we had to cope with the unexpected stability of the picolinoyl residue of PI as demonstrated by the following observations. For instance, extensive degradation of PI_A under basic or acidic conditions was known to lead to all the constitutive amino-acids except the 3-hydroxy-picolinic acid which remained attached to threonine[5]. Moreover, previous works on virginiamycin S (3), a close analogue of PI_A, had demonstrated that upon treatment with trifluoro acetic acid, the macrolactone was cleaved between the phenyl alanine and the 4-oxo-pipecolic residues[6]. Finally, degradation of PI_A by collision in mass spectroscopy had been shown to generate all the amino-acids fragments but the picolinic residue[7]. Nevertheless, in spite of these negative indications, we embarked upon a program aimed at the cleavage of this group and we report herein a successful approach to this problem based upon a simple and regioselective zinc reduction.

Initial attempts to convert the target amide of PI_A into an hydrolysable group using chlorinating reagents (PCl_5 or $POCl_3$) or Merwein's salts met with total failure. In a second series of endeavours, we designed more elaborated strategies featuring an internal delivery to the amide carbonyl of a nucleophile tethered to the nitrogen or the oxygen of the 3-hydroxy-picolinic moiety. These approaches were to no avail : in no cases were we able to detect a trace of the expected product (5). We then decided to investigate the electrochemical behaviour of (1) as it is known that certain amides can be reduced electrochemically[8], according to the following scheme for isonicotinamide :



Fleury *et al.* discovered that PI_A could be indeed electrochemically reduced under acidic conditions, at ca -0.9 V s.c.e., to afford (5) in 50 % yield along with numerous by-products[9]. We immediately looked for a chemical extrapolation of this reduction and zinc was selected as the reducing reagent since its reduction potential is -1 V s.c.e.. We were delighted to find that addition of zinc powder to a solution of (1) (*from a crude batch; estimated purity in pristinamycin I_A : 80%*) in aqueous HCl resulted in the rapid consumption of (1). Chromatography of the resulting mixture led to (5) in yields ranging from 30 to 40 %. These modest

yields were fully consistent with a more complete study of the electrochemical behaviour of PI_A and analogues which demonstrated the involvement of an original reduction mechanism proceeding through an electron transfer to the aromatic nucleus, this pathway being responsible for the occurrence of many side-reactions during these reductions[10]. Among these side-reactions, the major one led in both cases to compound (7). This compound[11], which was isolated in 7 % chromatographed yield in the chemical reduction, resulted from the formal reduction of the carbonyl of the picolinic amide into the corresponding methylene.



Rapid "screening" of the reduction conditions demonstrated that sonication reduced the reaction time to a few minutes whereas acetic acid was shown not to be acidic enough to allow the reduction to proceed. On the other hand, formic acid was a possible alternative to HCl but was abandoned since it generated mixtures difficult to purify. Zinc could be substituted for iron or magnesium, though in those cases, yields of (5) dropped to less than 20 %. Finally, the zinc reduction was found to proceed without event at the kilogram scale. Compound (5) is stable under neutral conditions and can even be recrystallized from toluene. Cleavage of the picolinoyl residue was also carried out with comparable success from PI_B (2) and virginiamycin S (3) as the substrates. The facility of all these reductions can be regarded as a consequence of the peculiar redox properties of the picolinoyl residue of PI. Moreover, the modest yields of these reactions are completely redeemed by the simplicity of our approach which is quite noteworthy, especially when considering the complexity of PI and the failures of more sophisticated strategies.

In conclusion, we have discovered that the 3-hydroxy picolinoyl residue of pristinamycin I_A and related compounds could be cleaved in modest yields into the corresponding amines by a simple zinc-mediated reduction under acidic conditions. Applications of these versatile amines to the synthesis of new antibiotics are underway in our laboratories.

Experimental : The following procedure is typical of the cleavage of pristinamycins I.

To a suspension of pristinamycin IA (1) (10 g; 10,9 mmoles) in 250 mL of water was added at 16°C, 22 mL of HCl 12N. After complete dissolution, zinc dust (5,3 g; 81 mmoles) was added in portions over 30 minutes and the resulting mixture was stirred for 1h at 16°C. CH_2Cl_2 (80 mL) was then added followed by aqueous NaOH until pH 5. The mixture was filtered on Celite, the layers separated and the aqueous layer subsequently extracted with 30 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and then

concentrated to leave a yellow solid. Purification of this residue by flash-chromatography (eluent : CH_2Cl_2 / MeOH, 95-5) afforded (5) (3,07 g, 37.5% yield) as a pale yellow powder. Recrystallization of this material from toluene led to an analytical sample[11] ; mp : 188°C ± 5°C; α_D : 43.8° (c=1.19; $CHCl_3$); R_f = 0.78 (CH_2Cl_2 / MeOH, 90-10). Further elution led to impure fractions of (7). This material was purified by two consecutive flash-chromatographies to give (7)[11] (0.65 g; 7% yield) as a white solid; mp : 190°C ± 5°C; R_f = 0.69 (CH_2Cl_2 / MeOH, 90-10).

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