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Reactivity of 1-(Des-3-Hydroxy-Picolinoyl) Pristinamycin I_A

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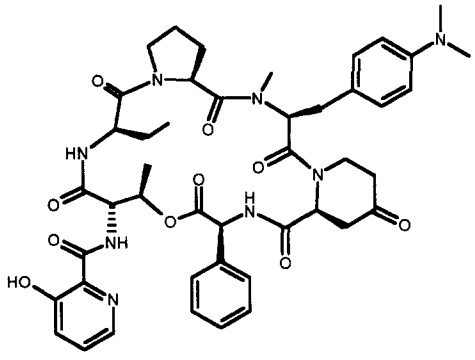
Abstract: 1-(Des-3-hydroxy-picolinoyl) pristinamycin I_A ($PI-NH_2$) was shown to undergo a variety of reactions, including two unexpected transformations, to afford new pristinamycin I_A derivatives.

Introduction

Pristinamycin is a naturally occurring antibiotic of the streptogramin class. This class of antibiotics is characterized by the original association of two types of chemically unrelated molecules, pristinamycins I (PI) and pristinamycins II (PII), which act synergistically on the ribosome of bacteria, thereby inhibiting protein synthesis.[1-4] Pristinamycins I, as typified by PI_A (the most abundant pristinamycin I), are cyclic depsipeptides, possessing an unusual 3-hydroxy picolinoyl exocyclic residue.



Pristinamycin I_A

After our discovery of Synercid®, the first injectable pristinamycin devised for the treatment of severe Gram positive infections in hospital,[5,6] we reported some years ago [7,8] the cleavage of the 3-hydroxy-picolinoyl residue of PI_A as a prelude to evaluating the importance of this residue [9] in the antibacterial activity of PI_A. We envisioned that condensation of 1-(des-3-hydroxy-picolinoyl) pristinamycin I_A (designated $PI-NH_2$) with various reagents would lead to original and biologically interesting PI_A derivatives (see Scheme I).

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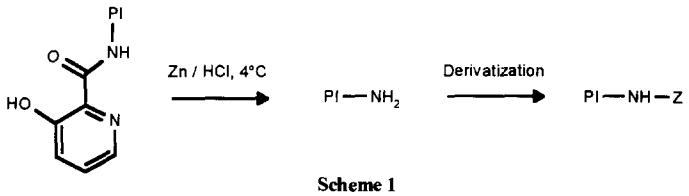
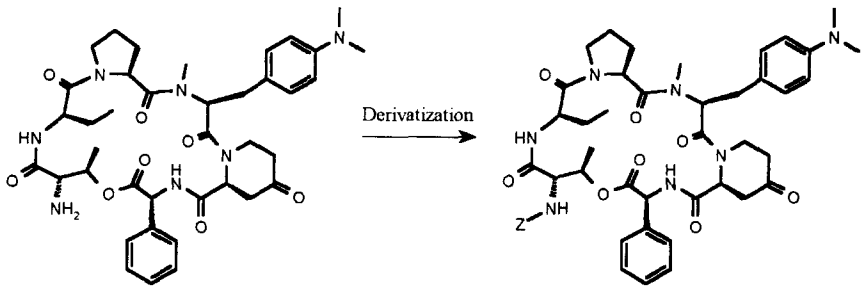


Scheme 1

Herafter, we report a summary of the results of a program aimed at exploring the reactivity of PI-NH_2. Condensations with acids (or acyl chorides), sulfonyl chlorides, chloroformates, isocyanates and isothiocyanates, as well as reductive aminations are described. Unexpected reactions observed during the course of this program will be also discussed.

Results and discussion

PI-NH_2 is a stable compound which can be recrystallized from toluene or stored, as an amorphous solid, for months at 4°C, without noticeable degradation. On the other hand, it was found to undergo a slow degradation in solution in polar solvents, at room temperature (see below the discussion about the unexpected reactions). Though PI-NH_2 proved to be a poorly reactive amine owing to the steric crowding around the nitrogen atom, it was nevertheless amenable to a wide range of transformations, albeit generally in modest yields. For instance, condensations with a slight excess of acyl chlorides, under standard conditions, were generally easy reactions which afforded modified PI_A derivatives in 5 to 70 % isolated yields.[7] PI-NH_2 could be condensed with carboxylic acids through activation as a mixed anhydride or by using a combination of HOBt and DCC (or EDCI [10]) as the coupling reagents.[7] However, for difficult condensations, DCC was clearly superior to EDCI.

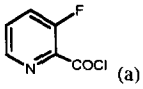
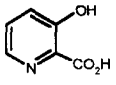
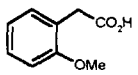
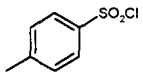


PI-NH_2

Whereas reactions with chloroformates afforded the corresponding carbamates in good yields, sulfonyl chlorides were less reactive and generated the expected sulfonamides in poor yields (< 30 %) or failed to deliver the expected compound. Isocyanates and isothiocyanates reacted smoothly with PI-NH_2 leading to the

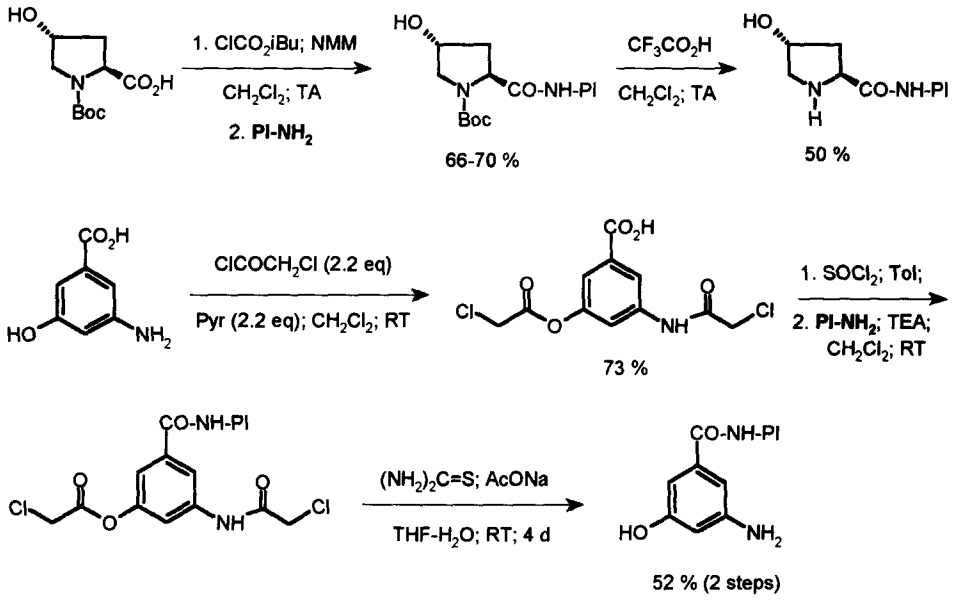
expected ureas (35 to 75 %) and thioureas (10 to 65 %) in good yields. Representative examples of these various reactions are shown in Table 1.

Table 1: Representative Examples of the Derivatization of PI-NH_2

Reagent	Conditions of condensation	Isolated yield (%)	Reagent	Conditions of condensation	Isolated yield (%)
PhCOCl	CH_2Cl_2; TEA; TA	47	$PhCH_2COCl$	CH_2Cl_2; TEA; TA	49
CH_3COCl	CH_2Cl_2; TEA; TA	38	 (a)	CH_2Cl_2; TEA; TA	62
	EDCI[5]; HOBt; CH_2Cl_2; TA	60 (b)		DCC; HOBt; CH_2Cl_2; TA	58
$ClCO_2Et$	TEA; THF; TA	62		Pyr.; TA	28
PhNCO	CH_2Cl_2; TA	63	$PhCH_2NCO$	CH_2Cl_2; TA	56
PhNCS	CH_2Cl_2; TA	62	Me-NCS	CH_2Cl_2; TA	50

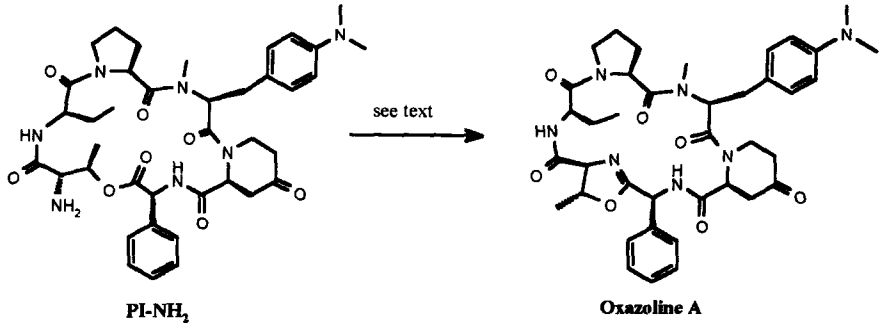
a: the corresponding acid was prepared by orthometallation, by analogy with ref. 11; see experimental section for details.
b: product identical to the natural product PI_A.

For those acids possessing a reactive hydroxyl group (eg phenol) or a free amino group, we had to choose protecting groups [12] compatible with the conditions of condensation of PI-NH_2 and easily removed from the resulting PIA derivatives, without jeopardizing the sensitive functions of the PI_A backbone. Basic conditions or hydrogenolysis for the deprotection step were rapidly turned down, owing to the anticipated problems caused, respectively, by the lactone and the ketone of PI_A. On the other hand, the Boc protecting group was shown to be well suited for our purpose, as demonstrated by the condensation of (4R)-4-hydroxy proline (see Scheme 2). However, the most versatile and appropriate protecting group was the chloroacetyl group: this group was easily attached to amines or alcohols possessing a carboxylic acid moiety, resisted to the preparation of the corresponding acyl chlorides and to the conditions of condensation with DCC and, most importantly, was readily removed, under almost neutral conditions, by aqueous thiourea.[13,14] As exemplified by the condensation of 3-amino-3-hydroxy benzoic acid which contains both functions (see Scheme 2), this strategy proceeded smoothly to deliver PI_A derivatives bearing a free amino and/or a phenolic hydroxyl group.



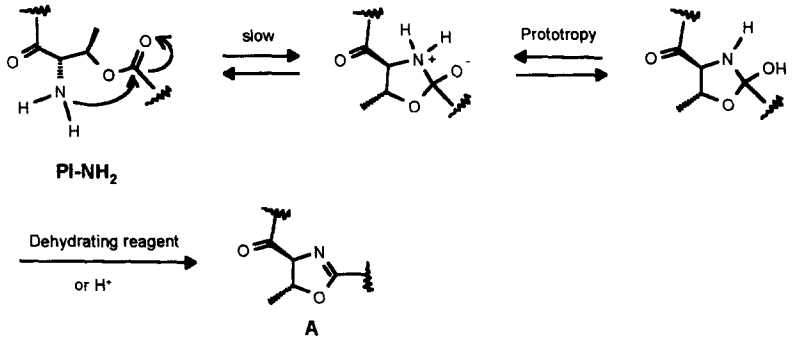
Scheme 2. An exemple of a condensation of PI-NH_2 with acids containing amino and/or hydroxyl groups.

During the course of our studies, we encountered two interesting reactions of PI-NH_2 which stemmed from the vicinity of the amino group with the lactone function. As a consequence of the steric hindrance around the nitrogen atom, condensation reactions of PI-NH_2 were occasionally very sluggish, especially in the case of DCC or EDCI coupling reactions with sterically hindered acids and condensations with poorly reactive acyl chorides or sulfonyl chlorides. In those slow condensations, whatever the solvent, we isolated a new derivative, along with the expected compound or as the only product of the reaction. This side-product was identified by spectroscopic analysis as oxazoline A (see Scheme 3).



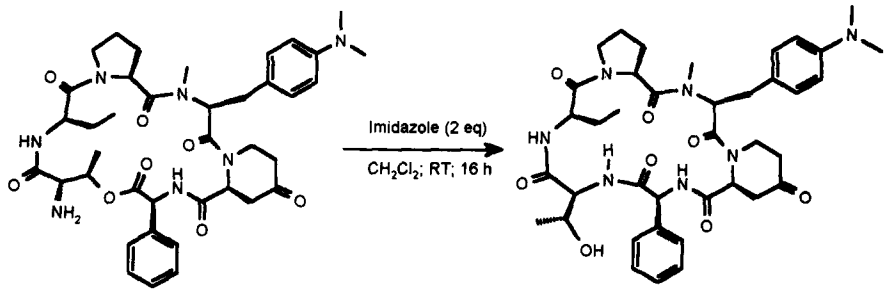
Scheme 3

For example, this compound was isolated in 48 % yield, as the only product of the reaction, in an attempted condensation of PI-NH_2 with tosyl chloride (1,1 eq), in the presence of pyridine (1,1 eq), in methylene chloride, at RT. This result was in sharp contrast with that observed when the same reaction was run in neat pyridine: in this case, only the expected sulfonamide was isolated (see table 1). We also observed that solutions of PI-NH_2 (without any other additives), when left on the bench for several days, slowly generated oxazoline A. Most of the usual «polar» solvents (chlorinated solvents, acetone, methanol, THF, acetonitrile...) were able to induce this transformation which was accelerated by an increase of temperature. For example, in refluxing dichloromethane, PI-NH_2 afforded, after 48 h, without further clear evolution, a 1/1 mixture of the expected oxazoline and of the starting material whereas, in refluxing chloroform or acetone, the expected conversion was complete within 4 days (quantitative yield). This derivative probably arose from an intramolecular cyclodehydration, facilitated by a trace of acid present in the solvents or by the dehydrating conditions of the coupling reaction mixtures (see Scheme 4). Both conditions convert the hydroxyl group of the intermediate orthoamide into a good leaving group.



Scheme 4. Suggested mechanism for the formation of oxazoline A

Another interesting compound was generated upon condensation of PI-NH_2 with a carboxylic acid when carbonyldiimidazole (CDI) was used as the activating reagent. The only PI_A derivative isolated in 56 % yield in this reaction was lactam B (Scheme 5). Based on a rapid mechanistic analysis of this reaction, we estimated that CDI could not be responsible for this rearrangement. We reasoned that imidazole, always present in old samples of CDI, had triggered this transamidification following the intramolecular attack of the amino group onto the lactone function, as already exemplified for other amino esters.[15, 16] We were delighted to find that the addition of imidazole to a solution of PI-NH_2 in methylene chloride, at RT, indeed induced the expected rearrangement. Rapid optimization of the reaction conditions on a 0.5 g scale revealed that 2 equivalents of imidazole were necessary for the fast and total conversion of the starting material. Under these conditions, lactam B could be isolated in 86 % yield.

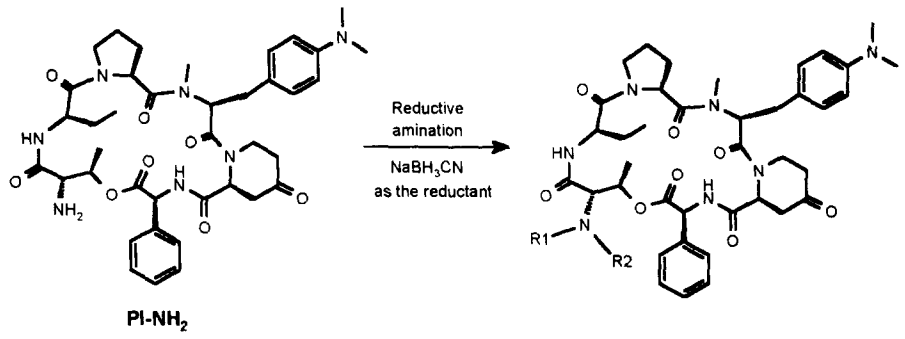


Scheme 5

However, the rate of this reaction was markedly decreased when the reaction was conducted with 5 g of PI-NH_2: the addition of a third equivalent of imidazole after 5 days, at RT, was necessary to complete the reaction within one day and to achieve a 90 % yield. We also discovered incidentally, during our endeavors to alkylate PI-NH_2 under basic conditions with alkyl halides (see below), that the above transamidification also proceeded in the presence of sodium bicarbonate, in methanol or methylene chloride (isolated yield of lactam B: 40 %).

With lactam B in hand, we decided to briefly investigate the reactivity of this compound. The free hydroxyl turned out to be poorly reactive owing to steric crowding in this region of the molecule. Thus, acylation with an excess of acetyl or benzoyl chloride in the presence of pyridine (neat or diluted by methylene chloride), at RT, proceeded sluggishly and afforded, after purification, the expected esters in disappointingly low yields (respectively 17 and 26 %). Furthermore, picolinoyl chloride could not be made to react, even in refluxing methylene chloride. 3-hydroxy picolinic acid was unreactive in the presence of EDCI and HOBt, whereas condensation with picolinic acid, DCC and catalytic DMAP only afforded a small amount of the expected ester which could not be separated from residual DCU.

We finally turned our attention toward the alkylation of PI-NH_2. Alkylations using alkyl halides under basic conditions met with total failure owing to the sensitivity of PI-NH_2 to bases (see above) and to alkylating reagents (formation of quaternary ammonium salts). On the other hand, reductive aminations were more rewarding, though complete purification of the resulting amines was often troublesome and incomplete (see Table 2).



Scheme 6

Table 2: Reductive Amination of PI-NH2

R_1	R_2	Aldehydes[a]	Conditions	Yield (%)	Remarks
Me	H	aq CH_2O	MeCN; 0°C; 4 h	17[b]	Incomplete purification; also detected the dimethylamino derivative and lactam B
Et	H	MeCHO	MeOH; AcONa; RT; 24 h	45[b]	No dialkylation; incomplete purification
Bn	H	PhCHO	Idem	4	Compound difficult to purify
i-Bu	H	iPr-CHO	Idem	50	-
$PhCH_2CH_2$	H	$PhCH_2CHO$	Idem	41	-
Me	Me	aq CH_2O	MeCN; RT; 24 h	26.5	Also formed lactam B

a: all the reductive aminations used $NaBH_3CN$ as the reductive reagent.

b: estimated yield based on the NMR purity

Whereas dimethylation of PI-NH_2 was difficult to avoid in the case of formaldehyde, exclusive monoalkylation was the rule for all the other aldehydes we used. As a reflect of this reactivity, attempts to prepare dialkylamino derivatives (in particular PI-NMeR) by a second reductive amination, starting from the monoalkylamino derivatives, were only successful in the case of the dimethylamino derivative (see table 2). Likewise, acylations of PI-NHR met with limited success. Condensations of PI-NHR (R = Me, Et or Bn) with 3-hydroxy picolinoyl acid (EDCI; CH_2Cl_2; RT) did not yield even a trace amount of the expected compounds. Reaction of PI-NHEt with benzoyl chloride afforded a trace of the expected compound whereas a similar condensation with PI-NHBn did afford the corresponding tertiary benzamide, but with an unacceptable purity.

In conclusion, we have explored the synthetic potential of 1-(des-3-hydroxy-picolinoyl) pristinamycin I_A (PI-NH_2). Despite its low reactivity, this amine underwent all the typical reactions of an usual amine, which allowed us to prepare a large array of new PI_A derivatives, some of which are described in the present paper. Biological activities of the compounds prepared during this program will be shortly reported and discussed in a forthcoming publication.

Experimental

Reagents and solvents were purchased from Prolabo or Janssen Chemica and used as supplied unless otherwise noted. PI-NH_2 was prepared according to reference.[8] Melting points were recorded on a Köfler apparatus and were not corrected. ^{1}H NMR spectra were recorded on Bruker AC 250 (250 MHz) or AM 400 (400 MHz) spectrometers. Chemical shifts (δ) are reported in ppm relative to internal tetramethylsilane. The atoms of pristinamycin I_A are numbered according to the method used by Anteunis and co-workers [17] for virginiamycin S. Infrared spectra (IR) were determined with a Perkin-Elmer Model 938G or 580B. Mass spectra (MS) were recorded on a NERMAG R10-10 spectrometer for electronic impact (EI; 70 eV), a FINNIGAN TSQ46 for desorption/chemical ionisation (DCI; ammonia as the reactant gas) and a VG AUTOSPEC for liquid secondary ion mass spectrometry (LSIMS; 35 KeV). Crude products were purified by flash column chromatography on silica gel (0.04-0.063 mm ; Merck). For thin layer chromatography (TLC), 250 mm E. Merck silica gel 60 F_{254} plates were used. Evaporations of PI derivatives were carried out below 35° C. In the experimental details hereafter, when the reaction flask is said to be equipped with a nitrogen inlet, it should be understood that the reaction was run under a nitrogen blanket. Combustion analyses for PI_A derivatives are rarely correct owing to the capacity of these compounds to sequester water and other solvents. However, corrections, based on the amount of water dosed in the product and that of solvents estimated from the ^{1}H NMR spectrum, may afford a good agreement with the expected figures. Hereafter will be given those results where agreement after correction has been reached. Melting points of PI derivatives (measured on a Köfler bank) are not generally sharp. The compounds sticks on the bank over several degrees. The figures indicated below for the melting points generally correspond to the temperature when sticking begins. .

1-Benzoyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A. In a 100 mL flask equipped with a magnetic bar, a nitrogen inlet, a thermometer and a bubbler were introduced 1 g of PI-NH_2 (1.34 mmol) and 20 mL of CH_2Cl_2. To the resulting solution 0.26 mL of TEA (1.61 mmol) and 0.17 mL of benzoyl chloride (1.48 mmol) were successively added. The reaction mixture was then stirred for 50 minutes at RT before quenching by the addition of 20 mL of water. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2x15 mL). The combined organic layers were washed with water (2x15 mL), dried over Na_2SO_4 and concentrated

under reduced pressure. The residue (1.1 g) was purified by flash-chromatography on silica gel (97/03 CH_2Cl_2 / MeOH v/v) to afford 0.75 g of 1-benzoyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A as a pale yellow solid (67 %). An analytical sample was obtained by stirring this solid in 20 mL of ether, followed by filtration and drying (recovered: 0.54 g; yield: 47 %); mp: 180°C.

^{1}H N.M.R. (250 MHz, $CDCl_3$, δ in ppm): 0.30 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.92 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; from 1.10 to 1.40 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.35 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.50 to 1.85 (m, 3H: the other H of CH_2 3γ and CH_2 2β) ; from 1.95 to 2.20 (m, 1H: the other H of CH_2 3β) ; from 2.05 to 2.35 (m, 3H: CH_2 5δ and the other H of CH_2 5β) ; 2.74 (dt, J = 13 and 4.5 Hz, 1H: 1H of CH_2 5ε) ; 2.90 (s, 6H: $ArN(CH_3)_2$) ; 2.92 and 3.26 (respectively dd and t, J = 12.5 and 4 Hz and J = 12.5 Hz, 1H each: CH_2 4β) ; 3.30 (s, 3H: NCH_3) ; 3.41 and 3.55 (2 m, 1H each: CH_2 3δ) ; 4.57 (dd, J = 8 and 6.5 Hz, 1H: CH 3α) ; 4.66 (broad dd, J = 13 and 8 Hz, 1H: the other H of CH_2 5ε) ; 4.85 (m, 1H: CH 2α) ; 4.92 (broad d, J = 6 Hz, 1H: CH 5α) ; 5.14 (dd, J = 10 and 1.5 Hz, 1H: CH 1α) ; 5.26 (dd, J = 12.5 and 4 Hz, 1H: CH 4α) ; 5.84 (d, J = 9.5 Hz, 1H: CH 6α) ; 5.90 (dq, J = 6.5 and 1.5 Hz, 1H: CH 1β) ; 6.57 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 6.58 (d, J = 10.5 Hz, 1H: CONH in 2) ; 6.90 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.15 to 7.35 (m, 5H: H Aromatics in 6α) ; 7.40 (d, J = 10 Hz, 1H: CONH in 1) ; 7.53 (t, J = 7.5 Hz, 2H: H Aromatics in meta of benzoyl) ; 7.64 (t, J= 7.5 Hz, 1H: H Aromatic in para of benzoyl) ; 7.88 (d, J= 7.5 Hz, 2H: H Aromatics in ortho of benzoyl) ; 8.57 (d, J = 9.5 Hz, 1H: CONH in 6). IR (KBr): 3425 ; 3280; 3000-2825; 2800; 1740; 1725;1680; 1650; 1520; 1245; 755; 700 cm^{-1}. MS (D/CI) M/z: 850 $(M+H)^+$; 832; 788; 728;273;188. Calculated for $C_{46}H_{55}N_7O_9$: C 65.0, H 6.52; N 11.54; Found: C 64.8; H 6.5; N 11.5 (corrected with 3 % of water).

1-Acetyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A was prepared according to the procedure described above, starting from 1 g of PI-NH_2 (1.34 mmol), 20 mL of CH_2Cl_2, 0.26 mL of TEA (1.61 mmol) and 0.1 mL of acetyl chloride (1.48 mmol). 0.4 g of 1-acetyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A was obtained (38 % yield). mp: 185 °C. ^{1}H N.M.R. (250 MHz, $CDCl_3$, δ in ppm): 0.32 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.91 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; from 1.10 to 1.35 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.28 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.50 to 1.85 (m, 3H: the other H of CH_2 3γ and CH_2 2β) ; 2.05 (m, 1H: the other H of CH_2 3β) ; from 2.10 to 2.35 (m, 3H: CH_2 5δ and the other H of CH_2 5β) ; 2.20 (s, 3H: $NCOCH_3$) ; 2.75 (dt, J = 13 and 4.5 Hz, 1H: 1H of CH_2 5ε) ; 2.86 (s, 6H: $ArN(CH_3)_2$) ; 2.94 and 3.32 (respectively dd and t, J = 12 and 3.5 Hz and J = 12 Hz, 1H each: CH_2 4β) ; 3.32 (s, 3H: NCH_3) ; from 3.40 to 3.65 (m, 2H: CH_2 3δ) ; 4.58 (dd, J = 7.5 and 6 Hz, 1H: CH 3α) ; 4.67 (broad dd, J = 13 and 8 Hz, 1H: the other H of CH_2 5ε) ; 4.79 (m, 1H: CH 2α) ; 4.88 (dd, J = 10 and 1.5 Hz, 1H: CH 1α) ; 4.92 (broad d, J = 6 Hz, 1H: CH 5α) ; 5.38 (dd, J = 12 and 3.5 Hz, 1H: CH 4α) ; 5.75 (dq, J = 6.5 and 1.5 Hz, 1H: CH 1β) ; 5.83 (d, J = 9.5 Hz, 1H: CH 6α) ; 6.38 (d, J = 10 Hz, 1H: CONH in 1) ; 6.60 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ;

6.74 (d, J = 9.5 Hz, 1H: CONH in 2) ; 7.05 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.15 to 7.35 (m, 5H: H Aromatics in 6α) ; 8.34 (d, J = 9.5 Hz, 1H: CONH in 6). IR (KBr): 3425 ; 3270; 3000-2825; 2800; 1725; 1680; 1650; 1520; 1245 cm^{-1}. MS (D/CI) M/z: 805 $(MNH_4)^+$; 788 $(M+H)^+$; 770. Calculated for $C_{41}H_{53}N_7O_9$: C 62.51, H 6.78; N 12.44; Found: C 62.2; H 6.8; N 12.3 (corrected with 3.4 % of water).

1-(Phenylacetyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A was prepared according to the procedure described above, starting from 1.5 g of PI-NH_2 (2 mmol), 0.68 mL of TEA (4.8 mmol), 30 mL of CH_2Cl_2, and 0.29 mL of phenylacetyl chloride (2.2 mmol). 0.85 g of 1-(phenylacetyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A was obtained (49 % yield). mp: 173 °C. ^1H N.M.R. (400 MHz, $CDCl_3$, δ in ppm): 0.30 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.89 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; from 1.05 to 1.20 (m, 1H: 1H of CH_2 3β) ; 1.11 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; 1.28 (m, 1H: 1H of CH_2 3γ) ; from 1.50 to 1.65 (m, 2H: the other H of CH_2 3γ and 1H of CH_2 2β) ; 1.71 (m, 1H: the other H of CH_2 2β) ; 2.05 (m, 1H: the other H of CH_2 3β) ; 2.15 (m, 1H: 1H of CH_2 5δ) ; from 2.20 to 2.35 (m, 2H: the other H of CH_2 5δ and the other H of CH_2 5β) ; 2.75 (dt, J = 13 and 4 Hz, 1H: 1H of CH_2 5ε) ; 2.82 (s, 6H: $ArN(CH_3)_2$) ; 2.92 and 3.28 (respectively dd and t, J = 12 and 4 Hz and J = 12 Hz, 1H each: CH_2 4β) ; 3.30 (s, 3H: NCH_3) ; 3.43 and 3.55 (2 m, 1H each: CH_2 3δ) ; 3.70 (AB, J = 14.5 Hz, 2H: $COCH_2Ar$) ; 4.56 (t, J = 7 Hz, 1H: CH 3α) ; 4.67 (broad dd, J = 13 and 7.5 Hz, 1H: the other H of CH_2 5ε) ; 4.78 (m, 1H: CH 2α) ; 4.86 (dd, J = 10 and 1.5 Hz, 1H: CH 1α) ; 4.95 (broad d, J = 6 Hz, 1H: CH 5α) ; 5.40 (dd, J = 12 and 4 Hz, 1H: CH 4α) ; 5.75 (dq, J = 6.5 and 1.5 Hz, 1H: CH 1β) ; 5.81 (d, J = 9 Hz, 1H: CH 6α) ; 6.41 (d, J = 10 Hz, 1H: CONH in 2) ; 6.46 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 6.75 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; 7.08 (d, J = 10 Hz, 1H: CONH in 1) ; from 7.15 to 7.45 (m, 10H: H Aromatics in 6α and H Aromatics of benzyl) ; 8.40 (d, J = 9 Hz, 1H: CONH in 6). IR (KBr): 3410; 3280; 3000-2825; 2800; 1730; 1680; 1650; 1515; 1245; 700 cm^{-1}. MS (LSIMS) M/z: 864 $(M+H)^+$. Calculated for $C_{47}H_{57}N_7O_9$: C 65.33, H 6.65; N 11.35; O: 16.67 Found: C 65.3; H 6.9; N 11.5; O 16.7 (corrected with 1 % of water).

3-Fluoro Picolinic acid. This product was prepared by analogy with the procedure described in ref. 5. In a 250 mL flask equipped with a magnetic bar, a nitrogen inlet, a thermometer, a dropping funnel and a bubbler, 3.54 g of diaza-1,4 bicyclo [2,2,2] octane (DABCO; 30.6 mmol) and 150 mL of dry ether were introduced. The resulting solution was cooled to -60°C and 19.1 mL of n-butyl lithium (1.6 M in hexane; 30.6 mmol) were added over 5 minutes. The reaction was stirred at -20°C for 1 hour and then cooled to -75°C. 3.0 g of 3-fluoro pyridine (30.6 mmol) in solution in 15 mL of ether were then added over 9 minutes. The yellow suspension was then stirred at -60°C for 1 hour and then cooled back to -75°C. Carbon dioxide (obtained from dried ice) was then bubbled through the resulting mixture for 30 minutes. The resulting pale yellow, cloudy mixture was then allowed to warm to -10°C over 20 minutes and then quenched by the addition of

water (90 mL). The aqueous layer was extracted with ether (50 mL) and the organic layers were then discarded. The pH of the aqueous layer was brought to 4 by addition of aqueous acetic acid. As the expected acid could not be extracted from the resulting mixture whatever the pH, 6.17 g of $Cu(OAc)_2$-H_2O were added. A precipitated blue solid was isolated by filtration and washed with water (3x10 mL). The resulting insoluble material was suspended in a mixture of 40 mL of CH_2Cl_2, 20 mL of EtOH and 7 mL of water. H_2S (from the decomposition of FeS by aqueous HCl) was passed through the resulting suspension for 25 minutes. A black insoluble solid was then eliminated by filtering the reaction mixture through a short pad of celite. The filtrate was concentrated and the residual pink solid was crystallized from a mixture EtOH/H_2O (80/20), to afford 2.1 g of 3-fluoro picolinic acid (49 % yield) as a pale pink solid.

IR (KBr): 3070; 3300; 2100; 1720; 1595; 1570; 1450; 1425; 1280; 1270; 1230; 1100; 865; 810 cm^{-1}. MS (EI) M/z: 142 $(M+H)^+$, 124, 97, 70.

In a similar run (scale x 2 compared to the procedure above), the final reaction mixture was stirred overnight at RT. A voluminous insoluble material formed which was isolated by filtration. This solid was washed with ether (2x50 mL) and dried under vacuum to afford 8.59 g of the lithium salt of 3-fluoro picolinic acid, as a white solid (91 % yield). mp > 280 °C.

1-(3-Fluoro-picolinoyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A. In a 10 mL flask equipped with a condenser closed by a bubbler, was suspended 0.5 g of 3-fluoro-picolinic acid prepared as described above (3.1 mmol) in 1 mL of thionyl chloride. After addition of two drops of DMF, the reaction mixture was refluxed for 0.5 hour. The homogeneous solution was concentrated under reduced pressure to afford a yellow oil. This material was used as was in the following step.

1-(3-fluoro-picolinoyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A was prepared according to the procedure described above for the condensation of PI-NH_2 with acyl chlorides. To a solution of 2 g of PI-NH_2 (2.41 mmol), 0.44 mL of TEA (3.1 mmol) in 40 mL of CH_2Cl_2 was added 3-fluoro-picolinoyl chloride (prepared as described above; 3.1 mmol) in solution in 5 mL of CH_2Cl_2. After work-up, the crude material was purified by filtration on a short pad of silica gel and then by crystallization from ethanol. The resulting white crystals were washed with 30 mL of ether and dried to afford 1.3 g of 1-(3-fluoro-picolinoyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A (62 % yield); mp: 260 °C. ^1H N.M.R. (250 MHz, $CDCl_3$, δ in ppm): 0.56 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.89 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; from 1.10 to 1.40 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.31 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.50 to 1.85 (m, 3H: the other H of CH_2 3γ and CH_2 2β) ; 2.00 (m, 1H: the other H of CH_2 3β) ; from 2.15 to 2.45 (m, 3H: CH_2 5δ and the other H of CH_2 5β) ; 2.80 (m, 1H: 1H of CH_2 5ε) ; from 2.80 to 3.00 (m, 1H: 1H of CH_2 4β) ; 2.90 (s, 6H: $ArN(CH_3)_2$) ; 3.26 (s, 3H: NCH_3) ; 3.30 (t, J = 12.5 Hz, 1H: the other H of CH_2 4β) ; from 3.25 to 3.45 and 3.53 (2 m, 1H each: CH_2 3δ) ; 4.56 (dd, J = 7.5 and 6 Hz, 1H: CH 3α) ; 4.73 (broad dd, J = 13.5 and 7 Hz, 1H: the other H of CH_2 5ε) ; 4.82 (m, 1H: CH 2α) ; 4.96 (dd, J = 10 and 1.5 Hz, 1H: CH 1α) ; 5.18 (dd, J = 12.5 and 4 Hz,

1H: CH 4α) ; 5.20 (broad d, J = 6 Hz, 1H: CH 5α) ; 5.86 (d, J = 9.5 Hz, 1H: CH 6α) ; 5.89 (dq, J = 6.5 and 1.5 Hz, 1H: CH 1β) ; 6.53 (d, J = 10 Hz, 1H: CONH in 2) ; 6.60 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 7.02 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.15 to 7.40 (m, 5H: H Aromatics in 6α) ; 7.60 (m, 1H: 1' H_5) ; 7.69 (td; J = 9 and 1,5 Hz, 1H: 1' H_4) ; 8.18 (broad d, J = 4.5 Hz, 1H: 1' H_6) ; 8.24 (d, J = 10 Hz, 1H: CONH in 1) ; 8.72 (d, J = 9.5 Hz, 1H: CONH in 6). IR (KBr): 3600; 3200; 2940; 2876; 2810; 1743; 1725; 1680; 1650; 1630; 1525; 1450; 1410; 1375; 1355; 1195; 815; 755; 700 cm^{-1}. MS (DCI) M/z: 869 $(M+H)^+$. Calculated for $C_{45}H_{53}FN_8O_9$: C 62.2, H 6.15; F 2.19; N 12.9; Found: C 62.0; H 6.3; F 2.2; N 12.9.

Pristinamycin I_A. In a 100 mL flask equipped with a magnetic bar, a dropping funnel with a nitrogen inlet, a thermometer and a bubbler, 1 g of PI-NH_2 (1.34 mmol), 0.19 g of 3-hydroxy picolinic acid (1.34 mmol), 0.018g of hydroxy benzotriazole (HOBt; 0.134 mmol) and 10 mL of CH_2Cl_2 were introduced. To the resulting solution cooled at 5°C was added, dropwise, over 25 minutes, 0.28 g of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide chlorhydrate (EDCI; 1.47 mmol) in 25 mL of CH_2Cl_2. The reaction mixture was then stirred at 5°C for 4 h and then at RT for 17 hours. At that point, 20 mL of water were added. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were washed with water (2x20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue (1.3 g) was purified by flash-chromatography on silica gel (97/03 CH_2Cl_2 / MeOH v/v) to afford 1.1 g of pristinamycin I_A which was stirred in 20 mL of ether, filtered and dried to leave 0.70 g (60 % yield). An analytical sample, obtained by crystallization from ethanol (0.2 g in 1.5 mL of solvent; crystallization yield: 84 %), was found to be identical, in all respects, to the natural product.

1-((2-Methoxy-phenyl)-acetyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A was prepared according to the procedure described above, starting from 1.5 g of PI-NH_2 (2 mmol), 0.33 g of 2-methoxy phenyl acetic acid (2 mmol), 0.03 g of HOBt (0.2 mmol) in 10 mL of CH_2Cl_2 and 0.46 g of dicyclohexyl carbodiimide (DCC; 2.2 mmol) dissolved in 25 mL of CH_2Cl_2. 1.05 g of 1-((2-methoxy-phenyl)-acetyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A was obtained (58 % yield). mp: 180°C. ^1H N.M.R. (250 MHz, $CDCl_3$, δ in ppm): 0.23 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.90 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; from 1.05 to 1.40 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.25 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.50 to 1.70 (m, 2H: the other H of CH_2 3γ and 1H of CH_2 2β) ; 1.72 (m, 1H: the other H of CH_2 2β) ; 2.03 (m, 1H: the other H of CH_2 3β) ; from 2.05 to 2.35 (m, 3H: CH_2 5δ and the other H of CH_2 5β) ; from 2.65 to 2.80 (m, 1H: 1H of CH_2 5ε) ; 2.74 (s, 6H: $ArN(CH_3)_2$) ; 2.91 and 3.31 (respectively dd and t, J = 12 and 3.5 Hz and J = 12 Hz, 1H each: CH_2 4β) ; 3.31 (s, 3H: NCH_3) ; from 3.35 to 3.65 (m, 2H: CH_2 3δ) ; 3.62 and 3.71 (2 d, J = 14.5 Hz, 1H each: $COCH_2Ar$) ; 3.85 (s, 3H: $ArOCH_3$) ; 4.60 (dd, J = 7 and 6 Hz, 1H: CH 3α) ; 4.67 (broad dd, J = 13.5 and 7.5 Hz, 1H: the other H of CH_2 5ε) ; 4.80 (m, 1H: CH 2α) ; 4.83 (dd, J = 10 and 1.5 Hz, 1H: CH 1α) ;

4.96 (broad d, J = 6 Hz, 1H: CH 5α) ; 5.40 (dd, J = 12 and 3.5 Hz, 1H: CH 4α) ; 5.76 (dq, J = 6.5 and 1.5 Hz, 1H: CH 1β) ; 5.82 (d, J = 9 Hz, 1H: CH 6α) ; 6.30 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 6.40 (d, J = 10 Hz, 1H: CONH in 2) ; 6.74 (d, J = 10 Hz, 1H: CONH in 1) ; 6.91 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; 6.96 (d, J = 7.5 Hz, 1H: H Aromatic in 3 of (methoxy-2 phenyl)acetyl 1) ; 7.03 (t, J = 7.5 Hz, 1H: H Aromatic in 5 of (methoxy-2 phenyl)acetyl 1) ; from 7.15 to 7.45 (m, 7H: H Aromatics in 6α - H Aromatics in 4 and 6 of (methoxy-2 phenyl)acetyl 1) ; 8.38 (d, J = 9 Hz, 1H: CONH in 6). IR (KBr): 3420; 3280; 3000-2825; 2840; 2810; 1740; 1725: 1685; 1650; 1520; 1245; 815; 755; 700 cm^{-1}. MS (LSIMS) M/z: 894 $(M+H)^+$. Calculated for $C_{48}H_{59}N_7O_{10}$: C 64.48, H 6.65; N 10.97; O: 17.9. Found: C 64.3; H 6.6; N 10.85; O 18.1 (corrected with 1.2 % of water and 2 % of CH_2Cl_2).

1-(Ethoxycarbonyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A. In a 250 mL flask equipped with a magnetic bar, a nitrogen inlet, a thermometer and a bubbler, 1.5 g of PI-NH_2 (2 mmol) and 60 mL of THF were introduced. To the resulting solution were successively added 0.19 mL of ethyl chloroformiate (2 mmol) and 0.28 mL of TEA (2 mmol). The reaction mixture was then stirred overnight at RT before partition between 300 mL of water and 50 mL of ethyl acetate. The layers were separated and the aqueous layer extracted with ethyl acetate (20 mL). The combined organic layers were washed with water (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash-chromatography on silica gel (97/03 CH_2Cl_2 / MeOH v/v) to afford a solid which was stirred in 20 mL of ether, then filtered and dried to yield 1.02 g of 1-(ethoxycarbonyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A, as a pale yellow solid (62 %). mp: 140 °C. ^1H N.M.R. (400 MHz, $CDCl_3$, δ in ppm, at a temperature of 333K): 0.48 (broad dd, J = 16 Hz, 1H: 1H of CH_2 5β) ; 0.92 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; from 1.10 to 1.35 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.34 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; 1.38 (t, J = 7.5 Hz, 3H: CH_3 of ethyl) ; from 1.50 to 1.60 (m, 1H: the other H of CH_2 3γ) ; 1.67 and 1.79 (2 m, 1H each: CH_2 2β) ; 2.03 (m, 1H: the other H of CH_2 3β) ; 2.14 (m, 1H: 1H of CH_2 5δ) ; 2.25 (very broad d, J = 16 Hz, 1H: the other H of CH_2 5δ) ; 2.28 (d, J=16Hz, 1H: the other H of CH_2 5β) ; 2.75 (dt, J = 13 and 4 Hz, 1H: 1H of CH_2 5ε) ; 2.86 (s, 6H: $ArN(CH_3)_2$) ; 2.98 and 3.32 (respectively dd and t, J = 12 and 4 Hz and J = 12 Hz, 1H each: CH_2 4β) ; from 3.25 to 3.40 (m, 1H: 1H of CH_2 3δ) ; 3.32 (s, 3H: NCH_3) ; 3.51 (m, 1H: the other H of CH_2 3δ) ; from 4.20 to 4.40 (m, 2H: $COOCH_2$ of ethyl) ; 4.47 (broad b, 1H: CH 1α) ; from 4.60 to 4.70 (m, 2H: the other H of CH_2 5ε and CH 3α) ; 4.77 (m, 1H: CH 2α) ; 5.01 (broad b , 1H: CH 5α) ; 5.27 (d, J = 10 Hz, 1H: CONH in 1) ; 5.39 (very broad b, 1H: CH 4α) ; 5.78 (q, J = 6.5 Hz, 1H: CH 1β) ; 5.82 (d, J = 9.5 Hz, 1H: CH 6α) ; 6.56 (d, J = 10 Hz, 1H: CONH in 2) ; 6.63 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 7.13 (broad d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.15 to 7.35 (m, 5H: H Aromatics in 6α) ; 8.35 (d, J=9.5 Hz, 1H: CONH in 6). IR (KBr): 3410; 3285; 3000-2825; 2810; 1725; 1680; 1650; 1524; 816 cm^{-1}. MS (D/CI) M/z: 835 $(M+NH_4)^+$;

818 $(M+H)^+$. Calculated for $C_{42}H_{55}N_7O_{10}$: C 61.68, H 6.78; N 11.99; O: 19.56. Found: C 61.3; H 7.0; N 12.0; O 19.2 (corrected with 1 % of water).

1-(4-Methylphenyl)sulfonyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A. In a 100 mL flask equipped with a magnetic bar and a bubbler, 1.5 g of PI-NH_2 (2 mmol), 10 mL of pyridine and 0.38 g of tosyl chloride (2,2 mmol) were successively introduced. The reaction mixture was stirred at RT for 24 h and then concentrated under reduced pressure. The residue was partitioned between 20 mL of water and 20 mL of CH_2Cl_2. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were washed with water (2x20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash-chromatography on silica gel (97/03 CH_2Cl_2 / MeOH v/v) to afford 0.75 g of 1-(4-methylphenyl)sulfonyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A (42 % yield). An analytical sample was obtained by stirring this solid in 20 mL of ether, followed by filtration and drying (recovered: 0.5 g; 28 %); mp: 228°C. ^1H N.M.R. (250 MHz, $CDCl_3$, δ in ppm): 0.40 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.83 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; 0.96 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; 1.11 (m, 1H: 1H of CH_2 3β) ; 1.30 (m, 1H: 1H of CH_2 3γ) ; 1.45 (m, 1H: the other H of CH_2 3γ) ; 1.58 (m, 2H: CH_2 2β) ; 2.02 (m, 1H: the other H of CH_2 3β) ; from 2.10 to 2.30 (m, 2H: CH_2 5δ) ; 2.32 (d, J = 16 Hz, 1H: the other H of CH_2 5β) ; 2.45 (s, 3H: $ArCH_3$) ; 2.72 (dt, J = 13 and 4.5 Hz, 1H: 1H of CH_2 5ε) ; 2.87 (s, 6H: $ArN(CH_3)_2$) ; 3.04 and from 3.20 to 3.40 (respectively dd and m, J = 11.5 and 3.5 Hz, 1H each: CH_2 4β) ; 3.31 (s, 3H: NCH_3) ; from 3.20 to 3.40 and 3.49 (2 m, 1H each: CH_2 3δ) ; 3.91 (dd, J = 10 and 1.5 Hz, 1H: CH 1α) ; 4.56 (t, J = 7.5 Hz, 1H: CH 3α) ; from 4.60 to 4.75 (m, 2H: the other H of CH_2 5ε and CH 2α) ; 5.13 (broad d, J = 6 Hz, 1H: CH 5α) ; 5.53 (dd, J = 11.5 and 3.5 Hz, 1H: CH 4α) ; 5.61 (m, 1H: CH 1β) ; 5.72 (d, J = 9.5 Hz, 1H: CH 6α) ; 6.59 (m, 1H: CONH in 1) ; 6.63 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 6.69 (d, J = 10 Hz, 1H: CONH in 2) ; 7.20 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.10 to 7.45 (m, 5H: H Aromatics in 6α) ; 7.39 and 7.79 (2 d, J = 8 Hz, 2H each: respectively H Aromatics in 3 and 5 and H Aromatics in 2 and 6 of (methyl-4 phenylsulfonyl)-1) ; 8.29 (d, J = 9.5 Hz, 1H: CONH in 6). IR (KBr): 3420; 3280; 3000-2825; 2800; 1730; 1680; 1650; 1520; 1330; 1245; 1160; 815; 750; 700 cm^{-1}. MS (D/CI) M/z: 900 $(M+H)^+$. Calculated for $C_{46}H_{57}N_7O_{10}S$: C 61.39, H 6.38; N 10.89; O: 17.78; S 3.56. Found: C 61.1; H 6.0; N 10.9; O 17.6; S 3.2 (corrected with 3.5 % of water).

1-Benzylcarbamoyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A. In a 100 mL flask equipped with a magnetic bar and a bubbler, 1.5 g of PI-NH_2 (2 mmol), 30 mL of CH_2Cl_2 and 0.32 g of benzyl isocyanate (2.4 mmol) were successively introduced. The reaction mixture was stirred at RT for 15 h and then quenched by the addition of 20 mL of water. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were washed with water (2x20 mL), dried over Na_2SO_4 and concentrated

under reduced pressure. The residue (1.8 g) was purified by flash-chromatography on silica gel (97/03 CH_2Cl_2 / MeOH v/v) to afford 1.4 g of 1-benzylcarbamoyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A (80 % yield). An analytical sample was obtained by stirring this solid in 20 mL of ether, followed by filtration and drying (recovered: 1.0 g; 56.5 %); mp: 174°C. ^1H N.M.R. (400 MHz, $CDCl_3$, δ in ppm): 0.25 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.92 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; 1.23 (m, 1H: 1H of CH_2 3β) ; from 1.25 to 1.40 (m, 1H: 1H of CH_2 3γ) ; 1.35 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.55 to 1.70 (m, 2H: the other H of CH_2 3γ and 1H of CH_2 2β) ; 1.85 (m, 1H: the other H of CH_2 2β) ; from 2.05 to 2.20 (m, 2H: the other H of CH_2 3β and 1H of CH_2 5δ) ; 2.20 (d, J = 16 Hz, 1H: the other H of CH_2 5β) ; 2.25 (broad d, J = 14,5 Hz, 1H: the other H of CH_2 5δ) ; 2.73 (dt, J = 13.5 and 4 Hz, 1H: 1H of CH_2 5ε) ; 2.86 (s, 6H: $ArN(CH_3)_2$) ; 2.91 and 3.26 (respectively dd and t, J = 12.5 and 3.5 Hz and J = 12.5 Hz, 1H each: CH_2 4β) ; 3.31 (s, 3H: NCH_3) ; 3.40 and 3.56 (2 m, 1H each: CH_2 3δ) ; from 4.40 to 4.60 (m, 3H: CH 3α and NCH_2Ar) ; 4.66 (broad dd, J = 13.5 and 7 Hz, 1H: the other H of CH_2 5ε) ; 4.82 (dd, J = 10 and 1.5 Hz, 1H: CH 1α) ; 4.85 (m, 1H: CH 2α) ; 4.96 (broad d, J = 6 Hz, 1H: CH 5α) ; 5.35 (dd, J = 12.5 and 3.5 Hz, 1H: CH 4α) ; 5.56 (t, J = 5.5 Hz, 1H: NCONH) ; 5.82 (dq, J = 6.5 and 1.5 Hz, 1H: CH 1β) ; 5.85 (d, J = 9.5 Hz, 1H: CH 6α) ; 5.93 (d, J = 10 Hz, 1H: CONH in 1) ; 6.55 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 6.87 (d, J = 10.5 Hz, 1H: CONH in 2) ; 7.03 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.15 to 7.50 (m, 10H: H Aromatics in 6α and H Aromatics of benzyl) ; 8.57 (d, J = 9.5 Hz, 1H: CONH in 6). IR (KBr): 3425 ; 3280; 3000-2825; 2800; 1735; 1725; 1680; 1650; 1630; 1520; 1245; 750; 700 cm^{-1}. MS (D/CI) M/z: 879 $(M+H)^+$; MS/MS M/z: 772; 675. Calculated for $C_{47}H_{58}N_8O_9$: C 64.22, H 6.65; N 12.75; O: 16.38. Found: C 64.1; H 6.6; N 12.8; O 16.2 (corrected with 4.5 % of water and 2.8 % of CH_2Cl_2).

1-Phenylcarbamoyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A was prepared according to the procedure described above, starting from 1.5 g of PI-NH_2 (2 mmol), 30 mL of CH_2Cl_2 and 0.26 mL of phenyl isocyanate (2.4 mmol). 1.1 g of 1-phenylcarbamoyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A was finally obtained (63 % yield). mp: 203 °C. ^1H N.M.R. (250 MHz, $CDCl_3$, δ in ppm): 0.28 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.89 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; from 1.15 to 1.45 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.38 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.50 to 1.80 (m, 3H: the other H of CH_2 3γ and CH_2 2β) ; from 2.00 to 2.30 (m, 4H: the other H of CH_2 3β - CH_2 5δ and the other H of CH_2 5β) ; 2.69 (dt, J = 13 and 4.5 Hz, 1H: 1H of CH_2 5ε) ; 2.84 (s, 6H: $ArN(CH_3)_2$) ; 2.97 and 3.28 (respectively dd and t, J = 12.5 and 4.5 Hz and J = 12.5 Hz, 1H each: CH_2 4β) ; 3.31 (s, 3H: NCH_3) ; from 3.40 to 3.65 (m, 2H: CH_2 3δ) ; 4.57 (dd, J = 8 and 6 Hz, 1H: CH 3α) ; 4.66 (broad dd, J = 13 and 7 Hz, 1H: the other H of CH_2 5ε) ; 4.78 (dd, J = 10 and 1.5 Hz, 1H: CH 1α) ; 4.82 (m, 1H: CH 2α) ; 4.95 (broad d, J = 6 Hz, 1H: CH 5α) ; 5.37 (dd, J = 12.5 and 4.5 Hz, 1H: CH 4α) ; 5.78 (m, 1H: CH 1β) ; 5.82 (d, J = 9.5 Hz, 1H: CH 6α) ; 5.99 (d, J = 10 Hz, 1H: CONH in 1) ; 6.56 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 6.82 (d, J = 10 Hz, 1H: CONH in 2) ; 7.03 (d, J =

8.5 Hz, 2H: H Aromatics 4δ) ; from 7.05 to 7.45 (m, 10H: H Aromatics in 6α and H Aromatics of anilino) ; 7.47 (s, 1H: NCONHAr) ; 8.62 (d, J = 9.5 Hz, 1H: CONH in 6). IR (KBr): 3425; 3280; 3000-2825; 2800; 1745; 1720; 1680; 1650; 1630; 1520; 1245; 750 ; 700 cm^{-1}. MS (D/CI) M/z: 865 $(M+H)^+$; 803; 772; 728. Calculated for $C_{46}H_{56}N_8O_9$: C 63.87, H 6.53; N 12.95; O 16.65 Found: C 63.5; H 6.8; N 12.7; O 16.6 (corrected with 1.7 % of water).

1-Phenylthiocarbamoyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A. In a 100 mL flask equipped with a magnetic bar and a bubbler, 1.5 g of PI-NH_2 (2 mmol), 30 mL of acetone and 0.29 mL of phenyl isothiocyanate (2.4 mmol) were successively introduced. The reaction mixture was stirred at RT for 24 h and then concentrated under reduced pressure. The residue (2.25 g) was purified by flash-chromatography on silica gel (97/03 CH_2Cl_2 / MeOH v/v) to afford 1.4 g of 1-phenylthiocarbamoyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A (79.5 % yield). An analytical sample was obtained by stirring this solid in 20 mL of ether, followed by filtration and drying (recovered: 1.1 g; 62 %); mp: 203°C. ^1H N.M.R. (250 MHz, $CDCl_3$, δ in ppm): 0.31 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.93 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; from 1.20 to 1.45 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.38 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.55 to 1.70 (m, 1H: the other H of CH_2 3γ) ; 1.73 (m, 2H: CH_2 2β) ; from 2.00 to 2.40 (m, 4H: the other H of CH_2 3β - CH_2 5δ and the other H of CH_2 5β) ; 2.64 (dt, J = 13 and 4.5 Hz, 1H: 1H of CH_2 5ε) ; 2.88 (s, 6H: $ArN(CH_3)_2$) ; 2.91 and 3.27 (respectively dd and t, J = 12 and 3.5 Hz and J = 12 Hz, 1H each: CH_2 4β) ; 3.32 (s, 3H: NCH_3) ; from 3.40 to 3.65 (m, 2H: CH_2 3δ) ; from 4.55 to 4.70 (m, 2H: CH 3α and the other H of CH_2 5ε) ; from 4.70 to 4.90 (m, 2H: CH 5α and CH 2α) ; 5.28 (very broad d, J = 12 Hz, 1H: CH 4α) ; 5.60 (very broad d, J = 10 Hz, 1H: CH 1α) ; 5.78 (d, J = 9 Hz, 1H: CH 6α) ; 5.80 (m, 1H: CH 1β) ; 6.46 (d, J = 9.5 Hz, 1H: CONH in 2) ; 6.60 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 6.83 (m, 1H: CONH in 1) ; 6.98 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.10 to 7.50 (m, 10H: H Aromatics in 6α and H Aromatics of anilino) ; 8.37 (s, 1H: NCSNHAr) ; 8.43 (d, J = 9 Hz, 1H: CONH in 6). IR (KBr): 3425; 3280; 3000-2825; 2800; 1735; 1725; 1680; 1650-1630; 1520; 1250; 755 ; 700 cm^{-1}. MS (LSIMS) M/z: 881 $(M+H)^+$. Calculated for $C_{46}H_{56}N_8O_8S$: C 62.7, H 6.41; N 12.72; O: 14.53; S 3.64. Found: C 63.0; H 6.4; N 12.9; O 14.1; S 3.9 (corrected with 2 % of water and 2.5 % of CH_2Cl_2).

1-Methylthiocarbamoyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A was prepared according to the procedure described above, starting from 2 g of PI-NH_2 (2.68 mmol), 20 mL of CH_2Cl_2 and 1.96 g of methyl isothiocyanate (26.8 mmol). 1.1 g of 1-methylthiocarbamoyl-1-(des-3-hydroxy picolinoyl) pristinamycin I_A was obtained (50 % yield). mp: 192 °C. ^1H N.M.R. (250 MHz, $CDCl_3$, δ in ppm): 0.29 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.91 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; from 1.10 to 1.40 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.33 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; 1.61 (m, 1H: the other H of CH_2 3γ) ; 1.69 (m, 2H: CH_2 2β) ;

from 2.05 to 2.35 (m, 3H: CH_2 5δ and the other H of CH_2 5β) ; 2.06 (m, 1H: the other H of CH_2 3β) ; 2.70 (dt, J = 13 and 4.5 Hz, 1H: 1H of CH_2 5ε) ; 2.85 (s, 6H: $ArN(CH_3)_2$) ; 2.96 and 3.27 (respectively dd and t, J = 12 and 4 Hz and J = 12 Hz, 1H each: CH_2 4β) ; 3.13 (d, J = 4 Hz, 3H: $CSNCH_3$) ; 3.28 (s, 3H: NCH_3) ; from 3.35 to 3.65 (m, 2H: CH_2 3δ) ; 4.53 (dd, J = 7.5 and 5.5 Hz, 1H: CH 3α) ; 4.66 (broad dd, J = 13 and 7 Hz, 1H: the other H of CH_2 5ε) ; 4.81 (m, 1H: CH 2α) ; 4.98 (broad d, J = 6 Hz, 1H: CH 5α) ; 5.34 (dd, J = 12 and 4 Hz, 1H: CH 4α) ; 5.60 (broad d, J = 9.5 Hz, 1H: CH 1α) ; 5.83 (d, J = 9 Hz, 1H: CH 6α) ; 5.83 (m, 1H: CH 1β) ; 6.58 (d, J = 9 Hz, 1H: CONH in 2) ; 6.62 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 6.78 (q, J = 4 Hz, 1H: NCSNH) ; 6.91 (broad b, 1H: CONH in 1) ; 7.09 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.10 to 7.35 (m, 5H: H Aromatics in 6α) ; 8.57 (d, J = 9 Hz, 1H: CONH in 6). IR (KBr): 3410; 3280; 3000-2825; 2800; 1730; 1680; 1650-1630; 1525; 1250; 755 ; 700 cm^{-1}. MS (LSIMS) M/z: 819 $(M+H)^+$. Calculated for $C_{48}H_{59}N_7O_{10}$: C 60.12, H 6.65; N 13.68; O: 15.63; S 3.92. Found: C 59.8; H 6.7; N 13.4; O 3.7 (corrected with 2 % of water).

1-((2S,4R)-N-tert-butoxycarbonyl-4-hydroxy-prolinoyl)-1-(des-3-hydroxypicolinoyl) pristinamycin I_A. In a 250 mL flask equipped with a magnetic bar, a dropping funnel with a nitrogen inlet, a thermometer and a bubbler, 0.31 g of (2S,4R)-N-tert-butoxycarbonyl-4-hydroxy-proline (1.34 mmol) was dissolved in 10 mL of anhydrous THF. To the resulting solution cooled at -20°C, 0.147 mL N-methyl morpholine (1.34 mmol) and 0.173 mL of isobutyl chloroformiate (1.34 mmol) were successively added. The reaction mixture was then stirred for 1 hour at -10°C. To the resulting solution warmed to 0°C, 1 g of PI-NH_2 (1.34 mmol) in 10 mL of a mixture of THF and CH_2Cl_2 (1/1 v/v) was rapidly added. The reaction mixture was then stirred at RT for 2 hours before partition between 20 mL of water and 40 mL of CH_2Cl_2. The organic layer was separated and the aqueous layer, after addition of solid $NaHCO_3$ up to pH 7, was extracted with 20 mL of CH_2Cl_2. The combined organic layers were washed with water (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue (1.27 g) was purified by flash-chromatography on silica gel (95/05 CH_2Cl_2 / MeOH v/v) to afford 0.9 g of 1-((2S,4R)-N-tert-butoxycarbonyl-4-hydroxy-prolinoyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A as a white solid (70 % yield). An analytical sample was obtained by stirring this solid in 20 mL of pentane, followed by filtration and drying (recovered: 0.65 g; 50.5%); mp: 200°C. ^1H N.M.R. (400 MHz, $CDCl_3$, at a temperature of 323K, δ in ppm): 0.49 (broad d, J = 16 Hz, 1H: 1H of CH_2 5β) ; 0.93 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; from 1.20 to 1.40 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.31 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.45 to 1.65 (m, 1H: the other H of CH_2 3γ) ; 1.50 (s, 9H: $C(CH_3)_3$) ; 1.67 and 1.74 (2 m, 1H each: CH_2 2β) ; from 2.20 to 2.30 (m, 5H: the other H of CH_2 3β - CH_2 5δ and CH_2 in β of prolyl) ; 2.42 (d, J = 16 Hz, 1H: the other H of CH_2 5β) ; 2.75 (m, 1H: 1H of CH_2 5ε) ; 2.87 (s, 6H: $ArN(CH_3)_2$) ; 3.00 and 3.28 (respectively dd and t, J = 12 and 4 Hz and J = 12 Hz, 1H each: CH_2 4β) ; 3.32 (s, 3H: NCH_3) ; from 3.40 to 3.60 (m, 2H: CH_2 3δ) ; 3.61 (broad s, 1H: OH) ; 4.50 (dd, J = 7 and 6 Hz, 1H:

CH 3α) ; from 4.55 to 4.75 (m, 6H: the other H of CH_2 5ε - CH 1α - CH_2 in δ of prolyl - CH in α of prolyl and CH in γ of prolyl) ; 4.73 (m, 1H: CH 2α) ; 5.05 (d, J = 6 Hz, 1H: CH 5α) ; 5.48 (dd, J = 12 and 4 Hz, 1H: CH 4α) ; 5.77 (q, J = 6.5 Hz, 1H: CH 1β) ; 5.94 (d, J = 9.5 Hz, 1H: CH 6α) ; 6.35 (broad d, J = 9 Hz, 1H: CONH in 2) ; 6.63 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 7.12 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.20 to 7.35 (m, 6H: H Aromatics in 6α and CONH in 1) ; 8.43 (d, J = 9.5 Hz, 1H: CONH in 6). IR (KBr): 3410; 3310; 3000-2870; 2805; 1740; 1725; 1685; 1650; 1520; 1245; 1165; 815; 700 cm^{-1}. MS (D/CI) M/z: 959 $(M+H)^+$. Calculated for $C_{49}H_{66}N_8O_{12}$: C 61.36, H 6.94; N 11.68; O 20.02. Found: C 61.4; H 7.0; N 11.7; O 20.0 (corrected with 1.5 % of water).

1-((2S,4R)-4-Hydroxy-prolinoyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A. In a 100 mL flask equipped with a magnetic bar and a bubbler, 1.43 g of 1-((2S,4R)-N-tert-butoxycarbonyl-4-hydroxy-prolinoyl)-1-(des-3-hydroxy picolinoyl) pristinamycin IA (1.49 mmol; prepared as described above), 15 mL of CH_2Cl_2 and 1.5 mL of trifluoroacetic acid were successively introduced. The resulting solution was stirred for 21 hours at RT before addition of 0.2 mL of trifluoroacetic acid to complete the reaction. After 6 more hours at RT, the reaction mixture was quenched at 0°C by the addition of solid $NaHCO_3$ and water (35 mL), and then diluted with 70 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (100 mL) and the combined organic layers successively washed with a 10% aqueous solution of $NaHCO_3$ (30 mL) and water (30 mL), before drying over $MgSO_4$, filtration and concentration under reduced pressure. The residue (1 g) was dissolved in 70 mL of water and 13 mL of HCl 0.1 N. The colorless solution was filtered to eliminate a few insoluble particles and then extracted twice with ethyl acetate (2x20 mL). The pH of the resulting aqueous layer was then adjusted to 7 by addition, at 0°C, of solid $NaHCO_3$. This mixture was extracted with 2x50 mL of CH_2Cl_2. The combined organic layers were washed with 20 mL of water, dried over $MgSO_4$, filtered and then concentrated under reduced pressure. The resulting white solid was recrystallized in 20 mL of ethyl acetate to afford 0.64 g of 1-((2S,4R)-4-hydroxy-prolinoyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A, as a white solid (50 % yield). mp: 256 °C. ^1H N.M.R. (400 MHz, $CDCl_3$, δ in ppm): 0.37 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.92 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; from 1.15 to 1.40 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.20 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.50 to 1.70 (m, 2H: the other H of CH_2 3γ and 1H of CH_2 2β) ; 1.72 (m, 1H: the other H of CH_2 2β) ; from 1.95 to 2.55 (m, 6H: the other H of CH_2 3β - CH_2 5δ - the other H of CH_2 5β and CH_2 in β of prolyl) ; 2.78 (dt, J = 13.5 and 4 Hz, 1H: 1H of CH_2 5ε) ; from 2.80 to 2.95 (m, 2H: CH_2 in δ of prolyl) ; 2.85 (s, 6H: $ArN(CH_3)_2$) ; 2.97 (dd, J = 12 and 4 Hz, 1H: 1H of CH_2 4β) ; from 3.20 to 3.40 (m, 2H: the other H of CH_2 4β and 1H of CH_2 3δ) ; 3.28 (s, 3H: NCH_3) ; 3.51 (m, 1H: the other H of CH_2 3δ) ; 4.26 and 4.46 (2m, 1H each: CH in α of prolyl and CH in γ of prolyl) ; 4.56 (t, J = 7.5 Hz, 1H: CH 3α) ; 4.65 (d, J = 10 Hz, 1H: CH 1α) ; from 4.65 to 4.80 (m, 2H: the other H of CH_2 5ε and CH 2α) ; 5.05 (broad d, J = 6 Hz, 1H: CH 5α) ; 5.27 (dd, J = 12 and 4 Hz, 1H: CH 4α) ; from 5.75

to 5.90 (m, 2H: CH 1β and CH 6α) ; 6.54 (d, J = 10 Hz, 1H: CONH in 2) ; 6.69 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 7.10 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.15 to 7.35 (m, 5H: H Aromatics in 6α) ; 8.19 (d, J = 10 Hz, 1H: CONH in 1) ; 8.66 (d, J = 10 Hz, 1H: CONH in 6). IR (KBr): 3420; 3280; 3000-2870; 2800; 1740; 1720; 1680; 1650; 1520; 1250; 815; 700 cm^{-1}. MS (D/CI) M/z: 859 $(M+H)^+$. Calculated for $C_{44}H_{58}N_8O_{10}$: C 61.51, H 6.81; N 13.05; O: 18.63. Found: C 61.2; H 6.7; N 12.7; O 18.2 (corrected with 2 % of water and 2.5 % of AcOEt).

3-Chloroacetamido-5-chloroacetoxy-benzoic acid. In a 250 mL flask equipped with a magnetic bar, a dropping funnel with a nitrogen inlet, a thermometer and a bubbler, 4.74 g of 3-amino-3-hydroxy benzoic acid (25 mmol), 60 mL of CH_2Cl_2 and 4.44 mL of pyridine (55 mmol) were introduced. To the resulting suspension cooled at 0°C, 4.38 mL of chloroacetyl chloride (55 mmol) in 10 mL of CH_2Cl_2 were added dropwise. The milky reaction mixture was then stirred for 18 hours at RT. The resulting thick white mixture was quenched by the addition of 70 mL of water and stirred for 3 hours before filtration. The insoluble material was thoroughly washed with several portions of CH_2Cl_2 and then dried to afford 5.6 g of pure 3-chloroacetamido-5-chloroacetoxy-benzoic acid as a white solid (73 % yield). ^1H N.M.R. (200 MHz, $(CD_3)_2SO$ d6, δ in ppm): 4.32 and 4.76 (2 s, 2H each: CH_2Cl) ; 7.50 - 7.84 and 8.08 (3 broad s, 1H each: H aromatics), 10.74 (broad s, 1H: ArNHCO). MS (EI) M/z: 305 $(M+H)^+$; 229;180;153;77.

1-(3-Amino-5-hydroxy-benzoyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A. In a 100 mL flask equipped with a magnetic bar and a condenser closed by a bubbler, 1.52 g of 3-chloroacetamido-5-chloroacetoxy-benzoic acid (5 mmol) was suspended in 25 mL of toluene. Following addition of 0.4 mL of thionyl chloride (5.5 mmol), the resulting suspension was refluxed for 1.5 hour to leave a dark orange solution and a small insoluble oily fraction. The supernatant toluenic solution was syringed out and then added, over 5 minutes, to a solution cooled at 0°C, of 1.5 g of PI-NH_2 (2 mmol), 1.4 mL of TEA (10 mmol) and 40 mL of CH_2Cl_2 in a 100 mL flask equipped with a magnetic bar, a bubbler and a nitrogen inlet. The resulting solution was allowed to return to RT and then stirred for 16 hours. At this point, 20 mL of water were added. The organic layer was separated, washed with water (2x30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to lead to 1.79 g of crude 1-(3-acetamido-5-acetoxy-benzoyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A, as a pink-orange solid.

In a 100 mL flask equipped with a magnetic bar and a bubbler, 1.52 g of thiourea (20 mmol), 0.68 g of sodium acetate trihydrate (5 mmol), 5 mL of water and a solution of 2.1 g of crude 1-(3-acetamido-5-acetoxy-benzoyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A in THF (30 mL) were successively introduced. The resulting homogeneous orange solution was stirred at RT for 4 days, until completion of the two deprotections. The reaction mixture, where a white insoluble precipitate has appeared, was then partitioned between water (15 mL) and CH_2Cl_2 (30 mL). The organic layer was separated, washed

successively with water (3x30 mL) and a saturated aqueous solution of $NaHCO_3$, filtered over $MgSO_4$ and concentrated under reduced pressure. The residue (1.2 g) was purified by flash-chromatography on silica gel (98/02 AcOEt/MeOH and then 95/05 AcOEt/MeOH v/v) to afford 0.91 g of 1-(3-amino-5-hydroxy-benzoyl)-1-(des-3-hydroxy picolinoyl) pristinamycin I_A, as a pale orange solid (global yield for two steps: 52 %). mp: 200°C. ^{1}H N.M.R. (250 MHz, $(CD_3)_2SO$ d6, δ in ppm): 0.50 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.82 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; from 1.15 to 1.40 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.17 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.45 to 1.75 (m, 3H: the other H of CH_2 3γ and CH_2 2β) ; from 2.00 to 2.20 (m, 4H: the other H of CH_2 3β - CH_2 5δ and the other H of CH_2 5β) ; from 2.60 to 2.75 (m, 1H: 1H of CH_2 5ε) ; 2.80 (s, 6H: $ArN(CH_3)_2$) ; from 2.95 to 3.20 (m, 2H: CH_2 4β) ; 3.21 (s, 3H: NCH_3) ; from 3.25 to 3.40 and 3.54 (2 m, 1H each: CH_2 3δ) ; 4.42 (m, 1H: the other H of CH_2 5ε) ; 4.64 (m, 1H: CH 2α) ; 4.72 (dd, J = 8.5 and 5 Hz, 1H: CH 3α) ; from 4.75 to 4.85 (m, 1H: CH 5α) ; 4.79 (broad d, J = 10 Hz, 1H: CH 1α) ; 5.04 (dd, J = 10 and 6 Hz, 1H: CH 4α) ; 5.13 (broad s, 2H: $ArNH_2$) ; 5.42 (dq, J = 6.5 and 1.5 Hz, 1H: CH 1β) ; 5.60 (d, J = 8.5 Hz, 1H: CH 6α) ; 6.30 - 6.43 and 6.56 (3 broad s, 1H each: H aromatics of amino 3 hydroxy 5 benzoylamino) ; 6.58 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 6.89 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.20 to 7.40 (m, 5H: H Aromatics in 6α) ; from 7.45 to 7.60 (m, 2H: CONH in 1 and CONH in 2) ; 8.49 (d, J = 8.5 Hz, 1H: CONH in 6) ; 9.23 (s, 1H: ArOH). IR (KBr): 3420; 3280; 3000-2870; 2800; 1735; 1720; 1685; 1620; 1520; 1245; 820; 700 cm^{-1}. MS (LSIMS) M/z: 881 $(M+H)^+$. Calculated for $C_{46}H_{56}N_8O_{10}$: C 62.71, H 6.41; N 12.72; O: 18.16. Found: C 62.7; H 6.1; N 12.4; O 16.0 (corrected with 4.6 % of water).

Oxazoline A.

By reaction of PI-NH_2 with TsCl: In a 100 mL flask equipped with a magnetic bar and a bubbler, 1.5 g of PI-NH_2 (2 mmol), 30 mL of CH_2Cl_2, 0.38 g of tosyl chloride (2.2 mmol) and 0.36 mL of pyridine (4.4 mmol) were successively introduced. The reaction mixture was stirred at RT for 21 h and then concentrated under reduced pressure. The residue was partitioned between 20 mL of water and 20 mL of CH_2Cl_2. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2x20 mL). The combined organic layers were washed with water (2x20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash-chromatography on silica gel (97/03 CH_2Cl_2 / MeOH v/v) to afford 1.3 g of oxazoline A (89 % yield). An analytical sample was obtained by stirring this solid in 20 mL of ether, followed by filtration and drying (recovered: 0.7 g; 48 %); mp: 184°C. ^{1}H N.M.R. (250 MHz, $CDCl_3$, δ in ppm): 0.22 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.99 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; 1.47 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.70 to 1.90 (m, 2H: 1H of CH_2 3β and 1H of CH_2 2β) ; from 1.90 to 2.25 (m, 6H: the other H of CH_2 2β - CH_2 3γ - CH_2 5δ and the other H of CH_2 5β) ; 2.32 (dt, J = 13 and 4 Hz, 1H: 1H of CH_2 5ε) ; 2.44 (m, 1H: the other H of CH_2 3β) ; 2.86 (s, 6H: $ArN(CH_3)_2$) ; 3.03 and 3.29 (respectively dd and t, J = 12 and 4 Hz and J = 12 Hz, 1H each: CH_2 4β) ; from 3.15 to 3.40 (m, 1H: 1H of CH_2 3δ) ; 3.43 (s, 3H: NCH_3) ; 3.63 (m, 1H: the other H

of CH_2 3δ) ; 4.25 (dd, J = 7.5 and 2.5 Hz, 1H: CH 1α) ; from 4.40 to 4.60 (m, 2H: the other H of CH_2 5ε and CH 2α) ; from 4.85 to 5.05 (m, 3H: CH 3α - CH 5α and CH 1β) ; 5.55 (dd, J = 12 and 4 Hz, 1H: CH 4α) ; 5.85(dd, J = 9.5 and 2.5 Hz, 1H: CH 6α) ; 6.61 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; from 7.05 to 7.40 (m, 8H: H Aromatics in 6α - CONH in 2 and H Aromatics 4δ) ; 9.16 (d, J = 9.5 Hz, 1H: CONH in 6). IR (CH_2Cl_2): 3667; 3400-3250; 2981; 2936; 2879; 2807; 1721; 1681; 1651; 1628; 1524; 1446; 1410; 1356; 816 cm^{-1}. MS (LSIMS) M/z: 728 $(M+H)^+$.

By thermal cyclization of PI-NH_2: In a 50 mL flask equipped with a magnetic bar and a condenser, 0.71 g of PI-NH_2 (0.95 mmol) was disolved in 25 mL of $CHCl_3$ on amylene. The resulting solution was refluxed for 4 days until complete disappearance of the starting material. The reaction mixture was concentrated to leave a yellow solid (0.73 g) which was shown by ^1H NMR to contain oxazoline A as the only detected PI_A (quantitative yield). An analytical sample was obtained following chromatography on silica gel (94/3/3 CH_2Cl_2/MeOH/CH_3CN), trituration in ether of the resulting solid, filtration and drying. Calculated for $C_{39}H_{49}N_7O_7$: C 64.35, H 6.79; N 13.47. Found: C 64.1; H 6.8; N 13.3 (corrected with 2.4 % of water). In a related run, 0.5 g PI-NH_2 (0.67 mmol) in 25 mL of acetone was transformed quantitatively, after 4 days at reflux, into oxazoline A.

Lactam B.

By reaction with imidazole: In a 100 mL flask equipped with a magnetic bar and a bubbler, 0.5 g of PI-NH_2 (0.67 mmol), 15 mL of CH_2Cl_2 and 0.091 g of imidazole (1.34 mmol) were successively introduced. The reaction mixture was stirred at RT overnight and then quenched by the addition of acetic acid (5 mL). The resulting solution was washed with water (2x20 mL) and the final organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was stirred in 20 mL of ether, followed by filtration and drying to afford 0.43 g (86% yield) of pure lactam B as a pale yellow solid. mp: 192-196°C.
In a related reaction, starting from 5 g of PI-NH_2 (6.7 mmol), 150 mL of CH_2Cl_2 and 0.913 g of imidazole (13.4 mmol), the conversion rate was estimated to be 50% after 2 days of reaction, and 80% after 5 days. Addition of 0.456 g of imidazole (6.7 mmol) allowed the completion of the reaction within one day. Following purification according to the same procedure as above, 4.5 g of lactam B were isolated (90 % yield). ^1H N.M.R. (400 MHz, $CDCl_3$, δ in ppm): 0.23 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.91 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; 1.06 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; 1.63 (m, 1H: 1H of CH_2 2β) ; from 1.85 to 2.10 (m, 6H: 1H of CH_2 3β - CH_2 3γ - the other H of CH_2 2β and CH_2 5δ) ; 2.12 (d, J = 16 Hz, 1H: the other H of CH_2 5β) ; 2.27 (m, 1H: 1H of CH_2 5ε) ; 2.42 (m, 1H: the other H of CH_2 3β) ; 2.86 (s, 6H: $ArN(CH_3)_2$) ; from 3.05 to 3.15 (m, 1H: 1H of CH_2 3δ) ; 3.11 and 3.21 (respectively dd and t, J = 12.5 and 4 Hz and J = 12.5 Hz, 1H each: CH_2 4β) ; 3.31 (broad b, 1H: OH) ; 3.41 (s, 3H: NCH_3) ; 3.60 (m, 1H: the other H of CH_2 3δ) ; 4.21 (d, J = 7.5 Hz, 1H: CH 1α) ; 4.37 (q, J = 6.5 Hz, 1H: CH 1β) ; 4.48 (m, 1H: the other H of CH_2

5ε) ; 4.62 (m, 1H: CH 2α) ; 4.79 (broad d, J = 6 Hz, 1H: CH 5α) ; 4.89 (dd, J = 9 and 5 Hz, 1H: CH 3α) ; 5.50 (dd, J = 12.5 and 4 Hz, 1H: CH 4α) ; 5.65 (d, J = 9 Hz, 1H: CH 6α) ; 6.23 (d, J = 7.5 Hz, 1H: CONH in 1) ; 6.62 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 7.14 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.15 to 7.40 (m, 6H: H Aromatics in 6α and CONH in 2) ; 9.80 (d, J = 9 Hz, 1H: CONH in 6). IR (KBr): 3600; 3200; 2935; ; 2875; 2800; 1725; 1675; 1635; 1525; 1450; 1410; 810; 750; 700 cm^{-1}. MS (LSIMS) M/z: 746 $(M+H)^+$. Calculated for $C_{39}H_{51}N_7O_8$: C 62.80, H 6.89; N 13.15; O: 17.16. Found: C 62.7; H 6.7; N 12.9; O 16.9 (corrected with 5.6 % of water).

By reaction with $NaHCO_3$:

In a 10 mL flask equipped with a magnetic bar and a bubbler, 0.1 g of PI-NH_2 (0.134 mmol), 1 mL of MeOH and 0.011 g of $NaHCO_3$ (0.134 mmol) were successively introduced. The reaction mixture was stirred at RT overnight until consumption of the starting material. The resulting mixture was partitioned between water (1 mL) and ethyl acetate (5 mL). The aqueous layer was extracted with ethyl acetate (3x3 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was stirred in 5 mL of ether, followed by filtration and drying to afford 0.04 g (40% yield) of lactam B as a pale yellow solid. Similar results were obtained in DMF or CH_2Cl_2.

Acylations of lactam B.

acetylation: In a 100 mL flask equipped with a magnetic bar, a nitrogen inlet, a thermometer and a bubbler, 0.3 g of lactam B (0.4 mmol) and 1 mL of CH_2Cl_2 were introduced. To the resulting solution, 0.72 mL of acetyl chloride (1 mmol) and 0.09 mL of pyridine (1.2 mmol) were successively added. The reaction mixture was then stirred overnight at RT before concentration under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with water (2x10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to leave a residue which was purified by flash-chromatography on silica gel (97/03 CH_2Cl_2 / MeOH v/v) to afford the expected ester. An analytical sample of this material was obtained by stirring this solid in 10 mL of ether, followed by filtration and drying (recovered: 0.053 g; 17 %); mp: 190°C. ^{1}H N.M.R. (400 MHz, $CDCl_3$, δ in ppm): 0.25 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.91 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; 1.23 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; 1.64 (m, 1H: 1H of CH_2 2β) ; from 1.80 to 2.10 (m, 6H: 1H of CH_2 3β - CH_2 3γ - the other H of CH_2 2β - CH_2 5δ) ; 1.87 (s, 3H: $OCOCH_3$) ; 2.13 (d, J = 16 Hz, 1H: the other H of CH_2 5β) ; 2.27 (m, 1H: 1H of CH_2 5ε) ; 2.42 (m, 1H: the other H of CH_2 3β) ; 2.87 (s, 6H: $ArN(CH_3)_2$) ; from 3.05 to 3.15 (m, 1H: 1H of CH_2 3δ) ; 3.11 and 3.21 (respectively dd and t, J = 12.5 and 4 Hz and J = 12.5 Hz, 1H each: CH_2 4β) ; 3.41 (s, 3H: NCH_3) ; 3.60 (m, 1H: the other H of CH_2 3δ) ; 4.33 (dd, J = 8 and 6.5 Hz, 1H: CH 1α) ; 4.48 (m, 1H: the other H of CH_2 5ε) ; 4.61 (m, 1H: CH 2α) ; 4.77 (broad d, J = 6 Hz, 1H: CH 5α) ; 4.88 (dd, J = 8 and 5 Hz, 1H: CH 3α) ; 5.37 (m, J = 6.5 Hz, 1H: CH 1β) ; 5.49 (dd, J = 12.5 and 4 Hz, 1H: CH 4α) ; 5.62 (d, J = 9 Hz, 1H: CH 6α) ; 6.03 (d, J = 8 Hz, 1H:

CONH in 1) ; 6.62 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 7.04 (d, J = 10 Hz, 1H: CONH in 2) ; from 7.05 to 7.40 (m, 7H: H Aromatics in 6α and H Aromatics 4δ) ; 9.79 (d, J = 9 Hz, 1H: CONH in 6). IR (KBr): 3410; 3280; 3000-2870; 2805; 1725; 1685; 1635; 1525; 1250; 815; 705 cm^{-1}. MS (D/CI) M/z: 788 $(M+H)^+$; 728.

benzoylation: In a 100 mL flask equipped with a magnetic bar, a nitrogen inlet, a thermometer and a bubbler, 0.5 g of lactam B (0.67 mmol) and 1.5 mL of pyridine were introduced. To the resulting solution, 0.26 mL of benzoyl chloride (2 mmol) was added. The reaction mixture was then stirred for 48 hours, at RT, before adding 15 mL of water and 5 mL of ethyl acetate. The pH of the aqueous layer was adjusted to pH 1 by addition of HCl 1N. The organic layer was discarded and the aqueous layer extracted by 5 mL of ethyl acetate. Solid $NaHCO_3$ was added to the resulting aqueous layer up to pH 7. Subsequent extraction by ethyl acetate (3x5 mL) yielded an organic layer which was dried over $MgSO_4$ and concentrated under reduced pressure. The residue left was purified by flash-chromatography on silica gel (97/03 CH_2Cl_2 / MeOH v/v) to afford 0.15 g of the expected ester (26 %); mp: 200°C. ^1H N.M.R. (300 MHz, $CDCl_3$, δ in ppm): 0.23 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.90 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; 1.37 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.55 to 1.75 (m, 1H: 1H of CH_2 2β) ; from 1.75 to 2.00 (m, 4H: 1H of CH_2 3β - CH_2 3γ - the other H of CH_2 2β) ; from 2.00 to 2.15 (m, 3H: CH_2 5δ and the other H of CH_2 5β) ; 2.24 (m, 1H: 1H of CH_2 5ε) ; 2.41 (m, 1H: the other H of CH_2 3β) ; 2.86 (s, 6H: $ArN(CH_3)_2$) ; from 3.00 to 3.20 (m, 2H: 1H of CH_2 3δ and 1H of CH_2 4β) ; 3.21 (t, J = 12Hz, 1H: the other H of CH_2 4β) ; 3.42 (s, 3H: NCH_3) ; 3.50 (m, 1H: the other H of CH_2 3δ) ; from 4.40 to 4.55 (m, 1H: the other H of CH_2 5ε) ; 4.50 (dd, J = 7.5 and 6.5 Hz, 1H: CH 1α) ; 4.60 (m, 1H: CH 2α) ; 4.77 (broad d, J = 6 Hz, 1H: CH 5α) ; 4.86 (dd, J = 8 and 5.5 Hz, 1H: CH 3α) ; 5.50 (dd, J = 12 and 4.5 Hz, 1H: CH 4α) ; 5.58 (d, J = 8.5 Hz, 1H: CH 6α) ; 5.70 (m, J = 6.5 Hz, 1H: CH 1β) ; 6.20 (d, J = 7.5 Hz, 1H: CONH in 1) ; 6.62 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 7.97 (d, J = 10 Hz, 1H: CONH in 2) ; from 7.05 to 7.45 (m, 9H: H Aromatics in 6α - H Aromatics 4δ and H aromatics in meta of benzoyl) ; 7.58 (t, J = 7.5 Hz, 1H: H aromatic in para of benzoyl) ; 7.65 (d, J = 7.5 Hz, 2H: H aromatics in ortho of benzoyl) ; 9.82 (d, J = 8.5 Hz, 1H: CONH in 6). IR (KBr): 3600-3250; 2975; 2937; 2879; 2808; 1722; 1685; 1668; 1647; 1632; 1524; 1440; 1411; 1355; 815 cm^{-1}. . MS (D/CI) M/z: 850 $(M+H)^+$; 728. Calculated for $C_{46}H_{55}N_7O_9$: C 65.00, H 6.52; N 11.54. Found: C 65.0; H 6.6; N 11.5; (corrected with 3.9 % of water).

N-Benzyl-1-(des-3-hydroxy-picolinoyl) pristinamycin I_A. In a 1L flask equipped with a magnetic bar and a bubbler, 10 g of PI-NH_2 (13.4 mmol), 250 mL of methanol, 2.2 g of anhydrous sodium acetate (26.8 mmol), 13.7 mL of benzaldehyde (13.4 mmol) and. 1.7 g of sodium cyanoborohydride (26.8 mmol) were successively introduced. The reaction mixture was stirred at RT (ca: 30°C) for 2.5 hours before concentration under reduced pressure. The residue was partitioned between water (200 mL) and CH_2Cl_2 (300 mL). The organic layer was extracted with CH_2Cl_2 (3x200 mL) and the combined organic layers washed with water

(3x200 mL). After decantation overnight, the organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Four consecutive flash-chromatographies on silica gel (97/03 CH_2Cl_2 / MeOH v/v) of the resulting residue were necessary to isolate 0.45g (4 % yield) of N-benzyl-1-(des-3-hydroxy-picolinoyl) pristinamycin I_A with a satisfactory purity. mp: 183°C. ^{1}H N.M.R. (250 MHz, $CDCl_3$, δ in ppm): 0.00 (dd, J = 16 and 5.5 Hz, 1H: 1H of CH_2 5β) ; 0.92 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; from 1.10 to 1.35 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.45 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; 1.58 (m, 1H: the other H of CH_2 3γ) ; 1.67 and from 1.75 to 1.95 (2 m, 1H each: CH_2 2β) ; from 1.95 to 2.25 (m, 3H: CH_2 5δ and the other H of CH_2 5β) ; 1.98 (m, 1H: the other H of CH_2 3β) ; 2.68 (dt, J = 13 and 4.5 Hz, 1H: 1H of CH_2 5ε) ; 2.70 and 3.14 (respectively dd and t, J = 12 and 3.5 Hz and J = 12 Hz, 1H each: CH_2 4β) ; 2.79 (s, 6H: $ArN(CH_3)_2$) ; 3.27 (s, 3H: NCH_3) ; 3.42 (d, J = 2 Hz, 1H: CH 1α) ; 3.58 (m, 2H: CH_2 3δ) ; 3.76 and 3.98 (2 d, J = 11 Hz, 1H each: NCH_2Ar) ; from 4.50 to 4.65 (m, 1H: the other H of CH_2 5ε) ; 4.60 (dd, J = 8.5 and 5.5 Hz, 1H: CH 3α) ; 4.67 (broad d, J = 5.5 Hz, 1H: CH 5α) ; from 4.75 to 4.95 (m, 1H: CH 2α) ; 4.82 (dd, J = 12 and 3.5 Hz, 1H: CH 4α) ; 5.74 (d, J = 9.5 Hz, 1H: CH 6α) ; 5.79 (dq, J = 6.5 and 2 Hz, 1H: CH 1β) ; 6.33 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 6.42 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.10 to 7.40 (m, 5H: H Aromatics in 6α) ; from 7.40 to 7.60 (m, 5H: H aromatics of benzyl) ; 8.01 (d, J = 10.5 Hz, 1H: CONH in 2) ; 8.62 (d, J = 9.5 Hz, 1H: CONH in 6). IR (KBr): 3425; 3280; 3000-2825; 2800; 1735; 1680; 1650; 1520; 1245; 755; 700 cm^{-1}. MS (LSIMS) M/z: 836 $(M+H)^+$. Calculated for $C_{48}H_{57}N_7O_8$: C 66.09, H 6.87; N 11.73; O: 15.31. Found: C 65.7; H 6.6; N 11.5; O 14.9 (corrected with 3 % of water).

In a similar run, starting from 12 g of PI-NH_2 (16.1 mmol), a single flash-chromatography (98/02 CH_2Cl_2 / MeOH v/v), followed by trituration in CH_2Cl_2 and then in pentane, afforded 3.95 g of N-benzyl-des-3-hydroxy-picolinoyl pristinamycin I_A whose purity was estimated to be 70 % by NMR (estimated yield: 20 %). This impure material was used for derivatization without further purification.

N-Methyl-1-(des-3-hydroxy-picolinoyl) Pristinamycin I_A. In a 100 mL flask equipped with a magnetic bar and a bubbler, 0.1 g of g of PI-NH_2 (0.131 mmol), 1 mL of acetonitrile, 0.015 g of sodium cyanoborohydride (0.2 mmol) were successively introduced. To the resulting solution cooled to 0°C, a solution of 0.01 mL of aqueous formaldehyde (37 % in water; 0.134 mmol) in 1 mL of acetonitrile was added dropwise. After addition, the reaction mixture was stirred for 1 hour before the addition of one drop of acetic acid, and then concentration under reduced pressure. The residue was partitioned between 5 mL of ethyl acetate and 3 mL of water. The organic layer was separated and dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash-chromatography on silica gel (98/02 CH_2Cl_2 / MeOH v/v) afforded 0.02 g of impure N-methyl-1-(des-3-hydroxy-picolinoyl) pristinamycin I_A (estimated purity by NMR: 85 %; estimated yield: 17 %). This material was used without further purification in attempted derivatizations. ^{1}H N.M.R. (300 MHz, $CDCl_3$, δ in ppm): 0.28 (dd, J = 16 and 5.5 Hz, 1H: 1H of CH_2 5β) ; 0.91 (t, J = 7.5 Hz, 3H: CH_3 2γ) ;

from 1.20 to 1.45 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.42 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.50 to 1.75 (m, 2H: the other H of CH_2 3γ and 1H of CH_2 in 2β) ; 1.80 (m, 1H: the other H of CH_2 2β) ; from 2.00 to 2.35 (m, 4H: the other H of CH_2 3β - CH_2 5δ and the other H of CH_2 5β) ; 2.58 (s, 3H: NCH_3 in 1α) ; 2.66 (dt, J = 13 and 4 Hz, 1H: 1H of CH_2 5ε) ; 2.85 (s, 6H: $ArN(CH_3)_2$) ; 2.96 (dd, J = 12 and 4 Hz, 1H: 1H of CH_2 4β) ; 3.12 (d, J = 1.5 Hz, 1H: CH 1α) ; from 3.25 to 3.60 (m, 3H: the other H of CH_2 4β and CH_2 3δ) ; 3.29 (s, 3H: NCH_3) ; 4.61 (dd, J = 8 and 5.5 Hz, 1H: CH 3α) ; from 4.60 to 4.70 (m, 1H: the other H of CH_2 5ε) ; 4.76 (m, 1H: CH 2α) ; 4.96 (broad b, 1H: CH 5α) ; 5.19 (dd, J = 12 and 4 Hz, 1H: CH 4α) ; 5.68 (dq, J = 6.5 and 1.5 Hz, 1H: CH 1β) ; 5.77 (d, J = 9 Hz, 1H: CH 6α) ; 6.60 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 7.10 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.10 to 7.35 (m, 5H: H Aromatics in 6α) ; 7.98 (d, J = 10.5 Hz, 1H: CONH in 2) ; 8.80 (d, J = 9 Hz, 1H: CONH in 6). MS (D/CI) M/z: 760 $(M+H)^+$; 728. Fractions of impure lactam B and of PI-NMe_2 were also isolated in the above chromatography.

N-Ethyl-1-(des-3-hydroxy-picolinoyl) Pristinamycin I_A was prepared according to the procedure described above for the preparation of the N-benzyl derivative, starting from 0.4 g of g of PI-NH_2 (0.54 mmol), 16 mL of methanol, 0.044 g of anhydrous sodium acetate (1.1 mmol), 0.1 mL of acetaldehyde (1.6 mmol) and 0.034 g of sodium cyanoborohydride (1.1 mmol) and stirring the reaction mixture at 0°C, for 2 hours. 0.25 g of N-ethyl-1-(des-3-hydroxy-picolinoyl) pristinamycin I_A was obtained after flash-chromatography on silica gel (95/05 CH_2Cl_2 / MeOH v/v). This material, whose purity was estimated to be close to 75 %, was used without further purification in the attempted derivatizations. ^1H N.M.R. (400 MHz, $CDCl_3$, δ in ppm): 0.30 (dd, J = 16 and 5.5 Hz, 1H: 1H of CH_2 5β) ; 0.91 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; 1.14 (t, J = 7 Hz, 3H: CH_3 of ethyl) ; from 1.25 to 1.45 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.40 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; from 1.55 to 1.70 (m, 1H: the other H of CH_2 3γ) ; 1.81 (m, 2H: CH_2 2β) ; from 1.90 to 2.10 (m, 1H: the other H of CH_2 3β) ; from 1.95 to 2.25 (m, 3H: CH_2 5δ and the other H of CH_2 5β) ; 2.66 (dt, J = 13 and 4 Hz, 1H: 1H of CH_2 5ε) ; 2.75 and from 2.80 to 2.95 (2 m, 1H each: NCH_2 of ethyl) ; 2.85 (s, 6H: $ArN(CH_3)_2$) ; 2.98 (dd, J = 12 and 4 Hz, 1H: 1H of CH_2 4β) ; 3.20 (broad s, 1H: CH 1α) ; from 3.20 to 3.35 (m, 1H: the other H of CH_2 4β) ; 3.29 (s, 3H: NCH_3) ; from 3.35 to 3.60 (m, 2H: CH_2 3δ) ; from 4.50 to 4.70 (m, 2H: CH 3α and the other H of CH_2 5ε) ; 4.74 (m, 1H: CH 2α) ; 4.98 (broad d, J = 5.5 Hz, 1H: CH 5α) ; 5.17 (dd, J = 12 and 4 Hz, 1H: CH 4α) ; 5.65 (broad q, J = 6.5 Hz, 1H: CH 1β) ; 5.73 (d, J = 9 Hz, 1H: CH 6α) ; 6.68 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 7.09 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.10 to 7.35 (m, 5H: H Aromatics in 6α) ; 7.99 (d, J = 10.5 Hz, 1H: CONH in 2) ; 8.78 (d, J = 9 Hz, 1H: CONH in 6). MS (D/CI) M/z: 774 $(M+H)^+$; 756; 746; 728.

N-Isobutyl-1-(des-3-hydroxy-picolinoyl) pristinamycin I_A was prepared according to the procedure described above for preparation of the N-benzyl derivative, starting from 6 g of g of PI-NH_2 (8 mmol), 100

mL of methanol, 1.32 g of anhydrous sodium acetate (8 mmol), 7.28 mL of isobutyraldehyde (8 mmol) and 1.0 g of sodium cyanoborohydride (16 mmol) and stirring the reaction mixture at RT, for 2.5 hours. 5.75 g of a pale yellow oil were obtained after flash-chromatography on silica gel (95/05 CH_2Cl_2 / MeOH v/v). An analytical sample of N-isobutyl-1-(des-3-hydroxy-picolinoyl) pristinamycin I_A was obtained by stirring this material in 50 mL of ether. The resulting solid was filtered and stirred again in 3x20 mL of pentane, followed each time by filtration. Drying finally afforded 2.9 g (50 %) of the expected compound as a white solid; mp: 212°C. ^{1}H N.M.R. (250 MHz, $CDCl_3$, δ in ppm): 0.32 (dd, J = 16 and 5.5 Hz, 1H: 1H of CH_2 5β) ; 0.92 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; 1.02 (d, J = 7 Hz, 6 H: 2 CH_3 of isobutyl) ; from 1.20 to 1.45 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.42 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; 1.62 (m, 1H: the other H of CH_2 3γ) ; from 1.65 to 1.75 (m, 1H: CH of isobutyl) ; 1.77 (m, 2H: CH_2 2β) ; 2.05 (m, 1H: the other H of CH_2 3β) ; from 2.05 to 2.35 (m, 3H: CH_2 5δ and the other H of CH_2 5β) ; 2.51 and 2.73 (2 dd, respectively J = 11 and 5.5 Hz and J = 11 and 6.5 Hz, 1H each: NCH_2 of isobutyl) ; 2.70 (dt, J = 13 and 4.5 Hz, 1H: 1H of CH_2 5ε) ; 2.87 (s, 6H: $ArN(CH_3)_2$) ; 2.98 and 3.30 (respectively dd and t, J = 12 and 4 Hz and J = 12 Hz, 1H each: CH_2 4β) ; 3.22 (d, J = 2 Hz, 1H: CH 1α) ; 3.30 (s, 3H: NCH_3) ; from 3.30 to 3.65 (m, 2H: CH_2 3δ) ; 4.60 (dd, J = 8 and 5 Hz, 1H: CH 3α) ; from 4.60 to 4.80 (m, 2H: the other H of CH_2 5ε and CH 2α) ; 5.03 (broad d, J = 5.5 Hz, 1H: CH 5α) ; 5.18 (dd, J = 12 and 4 Hz, 1H: CH 4α) ; 5.69 (dq, J = 6.5 and 2 Hz, 1H: CH 1β) ; 5.78 (d, J = 9.5 Hz, 1H: CH 6α) ; 6.60 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 7.07 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.10 to 7.35 (m, 5H: H Aromatics in 6α) ; 7.99 (d, J = 10 Hz, 1H: CONH in 2) ; 8.79 (d, J = 9.5 Hz, 1H: CONH in 6). IR (KBr): 3425; 3280; 3000-2825; 2800; 1735; 1680; 1650; 1520; 1245; 755; 700 cm^{-1}. MS (D/CI) M/z: 802 $(M+H)^+$. Calculated for $C_{43}H_{59}N_7O_8$: C 64.40, H 7.41; N 12.23; O: 15.96. Found: C 64.7; H 7.2; N 11.8; O 16.0 (corrected with 2.3 % of water and 4 % of CH_2Cl_2).

N-(2-Phenylethyl)-1-(des-3-hydroxy-picolinoyl) pristinamycin I_A was prepared according to the procedure described above for preparation of the N-benzyl derivative, starting from 1.5 g of PI-NH_2 (2 mmol), 30 mL of methanol, 0.33 g of anhydrous sodium acetate (4 mmol), 4.8 g of phenylacetaldehyde (50 % in diethyl phtalate; 2 mmol) and 0.25 g of sodium cyanoborohydride (4 mmol) and stirring the reaction mixture at RT for 2 hours. 1.15 g of N-(2-phenylethyl)-1-(des-3-hydroxy-picolinoyl) pristinamycin I_A was obtained after flash-chromatography on silica gel (97/03 CH_2Cl_2 / MeOH v/v). An analytical sample was obtained by successively stirring this solid in 15 mL of ether and twice in 20 mL of pentane, followed each time by filtration. Drying finally afforded 0.7 g (41 %) of the expected compound; mp: 163°C. ^{1}H N.M.R. (250 MHz, $CDCl_3$, δ in ppm): 0.32 (dd, J = 16 and 6 Hz, 1H: 1H of CH_2 5β) ; 0.92 (t, J = 7.5 Hz, 3H: CH_3 2γ) ; 1.25 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; 1.33 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; from 1.55 to 1.95 (m, 3H: the other H of CH_2 3γ and CH_2 2β) ; from 1.95 to 2.35 (m, 4H: the other H of CH_2 3β - CH_2 5δ and the other H of CH_2 5β) ; from 2.60 to 3.25 (m, 6H: 1H of CH_2 5ε - NCH_2CH_2Ar and 1H of CH_2 4β) ; 2.80

(s, 6H: $ArN(CH_3)_2$) ; 3.23 (d, J = 2 Hz, 1H: CH 1α) ; 3.31 (s, 3H: NCH_3) ; 3.31 (t, J = 12 Hz, 1H: the other H of CH_2 4β) ; from 3.40 to 3;65 (m, 2H: CH_2 3δ) ; from 4.60 to 4.85 (m, 2H: the other H of CH_2 5ε and CH 2α) ; 4.62 (dd, J = 8 and 5 Hz, 1H: CH 3α) ; 5.04 (broad d, J = 6 Hz, 1H: CH 5α) ; 5.24 (dd, J = 12 and 4 Hz, 1H: CH 4α) ; 5.65 (dq, J = 6.5 and 2 Hz, 1H: CH 1β) ; 5.86 (d, J = 9 Hz, 1H: CH 6α) ; 6.50 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 7.04 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.10 to 7.50 (m, 10H: H Aromatics in 6α and H Aromatics of phenyl) ; 7.90 (d, J = 10 Hz, 1H: CONH in 2) ; 8.79 (d, J = 9 Hz, 1H: CONH in 6). IR (KBr): 3425; 3280; 3000-2825; 2800; 1735; 1680; 1650; 1520; 1245; 755; 700 cm^{-1}. MS (LSIMS) M/z: 850 $(M+H)^+$. Calculated for $C_{47}H_{59}N_7O_8$: C 66.41, H 7.00; N 11.53. Found: C 66.8; H 6.9; N 10. 5 (corrected with 2.7 % of water).

N,N-Dimethyl-1-(des-3-hydroxy-picolinoyl) pristinamycin I_A was prepared according to the procedure described above for preparation of the N-methyl derivative, starting from 0.2 g of PI-NH_2 (0.27 mmol), 0.8 mL of acetonitrile, 0.1 mL of aqueous formaldehyde (37 % in water; 1.34 mmol) and 0.025 g of sodium cyanoborohydride (0.4 mmol) and stirring the reaction mixture at RT for 24 hours. 0.055 g of N,N-dimethyl-1-(des-3-hydroxy-picolinoyl) pristinamycin I_A (26.5 %) was obtained after flash-chromatography on silica gel (97/03 CH_2Cl_2 / MeOH v/v). ^1H N.M.R. (400 MHz, $CDCl_3$, δ in ppm): 0.26 (dd, J = 16 and 5.5 Hz, 1H: 1H of CH_2 5β) ; 0.93 (t, J=7.5 Hz, 3H: CH_3 2γ) ; 1.18 (m, 2H: 1H of CH_2 3β and 1H of CH_2 3γ) ; 1.46 (d, J = 6.5 Hz, 3H: CH_3 1γ) ; 1.53 (m, 1H: the other H of CH_2 3γ) ; 1.65 and 1.79 (2 m, 1H each: CH_2 2β) ; 1.97 (m, 1H: the other H of CH_2 3β) ; from 2.05 to 2.20 (m, 1H: 1H of CH_2 5δ) ; 2.17 (d, J = 16 Hz, 1H: the other H of CH_2 5β) ; 2.27 (broad d, J = 16Hz, 1H: the other H of CH_2 5δ) ; 2.68 (s, 6H: $N(CH_3)_2$) ; 2.80 (dt, J = 13 and 4 Hz, 1H: 1H of CH_2 5ε) ; 2.87 (s, 6H: $ArN(CH_3)_2$) ; 2.96 and 3.27 (respectively dd and t, J = 12 and 4 Hz and J = 12 Hz, 1H each: CH_2 4β) ; 3.27 (s, 3H: NCH_3) ; 3.41 (d, J = 1.5 Hz, 1H: CH 1α) ; 3.53 (m, 2H: CH_2 3δ) ; 4.56 (dd, J = 8 and 5.5 Hz, 1H: CH 3α) ; 4.68 (broad dd, J = 13.5 and 7 Hz, 1H: the other H of CH_2 5ε) ; 4.76 (broad d, J = 5.5 Hz, 1H: CH 5α) ; 4.80 (m, 1H: CH 2α) ; 5.10 (dd, J = 12 and 4 Hz, 1H: CH 4α) ; 5.76 (d, J = 9 Hz, 1H: CH 6α) ; 5.88 (dq, J = 6.5 and 1.5 Hz, 1H: CH 1β) ; 6.62 (d, J = 8.5 Hz, 2H: H Aromatics 4ε) ; 7.04 (d, J = 8.5 Hz, 2H: H Aromatics 4δ) ; from 7.15 to 7.35 (m, 5H: H Aromatics in 6α) ; 7.85 (d, J = 10 Hz, 1H: CONH in 2) ; 8.67 (d, J = 9 Hz, 1H: CONH in 6). MS (D/CI) M/z: 774 $(M+H)^+$. Lactam B and a trace of PI-NHMe were also detected in this reaction.

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