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ELECTROCHEMICAL REDUCTION OF PRISTINAMYCIN I_A AND RELATED STREPTOGRAMINS IN AQUEOUS ACIDIC MEDIUM.

M. Largeron[#], M. Vuilhorgne[o], I. Le Potier[#], N. Auzeil[#], E. Bacqué[o], J.M. Paris[o] and M.B. Fleury[#]*.

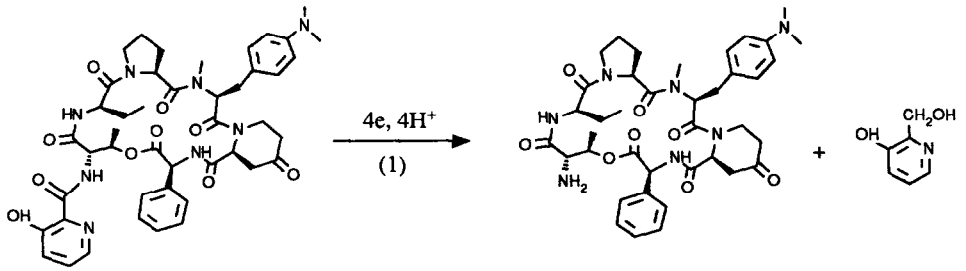
[#]Laboratoire de Chimie Analytique, URA CNRS 1310, Faculté de Pharmacie, 4 Avenue de l'Observatoire, 75270 Paris Cedex 06, France.

[o]Rhone-Poulenc-Rorer, Centre de Recherches de Vitry Alfortville, 13 quai Jules Guesde, 94403 Vitry sur Seine Cedex, France.

Abstract *- The electrochemical reduction of the picolinoyl residue of pristinamycin I_A and related streptogramins was performed at a mercury cathode, in aqueous acidic medium. The presence of a peptidic lactone residue at the amide nitrogen atom markedly modified the expected cathodic behaviour of pyridyl carboxamides: in particular, we observed the reduction of the pyridyl ring into tetrahydropyridine derivatives. Thanks to a series of model heterocyclic carboxamides, increasing steric hindrance at the amide nitrogen position was shown to lead to enhanced reduction of the heterocyclic ring.*

Pristinamycin is an antibiotic which is used in human therapeutic in severe Gram positive infections[1,2]. This antibiotic of the streptogramin family is an association of two groups of components, pristinamycin I and pristinamycin II, which exerts a synergistic inhibitory action on susceptible organisms. Pristinamycin I is a mixture of three peptidic macrolactones; the major component of this group is pristinamycin I_A **1** [eqn. (1)].

To gain a better understanding of the effect exerted by the 3-hydroxypicolinoyl residue of **1** on the pharmacological activity of pristinamycin, the cleavage of the corresponding amide was identified as the easiest pathway to modify this part of the molecule. A wide range of chemical methods met with failure[3] demonstrating that the conversion of **1** into the des-(3-hydroxypicolinoyl)-pristinamycin I_A (M-NH_2) was a difficult problem. Consequently, we turned our attention towards electrochemical methods in order to produce M-NH_2 as follows:



Pristinamycin I_A **1** (M)NH_2

The cathodic behaviour of various carboxylic amides R^1-CO-NH-R^2 has been the subject of many investigations, both in protic[4-13] and aprotic media[14-23]. The conclusions point to the fact that the reduction of carboxamides normally results in the formation of the corresponding amines[4] R^1-CH_2-NH-R^2. In a significant number of cases however, reductive cleavage of the C-N bond occurs to yield an aldehyde and / or an alcohol, along with the amine R^2-NH_2 derived from the splitting process. For instance, the electrochemical reduction of isonicotinamide was studied in aqueous media as a function of pH. In acidic solutions, the major product of the isonicotinic amide reduction was reported to be the aldehyde[10]. If the reduction proceeded further, the corresponding alcohol became the major product[7]. In neutral solutions, no aldehyde was apparently formed, even at the intermediate stage of the reduction and the major product was reported to be the alcohol. Isonicotinanilide R^1-CO-NH-C_6H_5 was remarkable in that it was the sole substituted pyridyl carboxamide which was found to prefer elimination of water (C-O bond splitting) instead of C-N bond cleavage, to yield the corresponding anilinomethylpyridine as the major product. At a more negative potential, the latter was reductively cleaved to the corresponding amine and γ-picoline[7].

In this context, the electrochemical reduction of pristinamycin I_A **1** was performed at the mercury electrode, in aqueous acidic solutions. M-NH_2 was successfully produced[24] in 50% yield according to equation (1). However, other electrochemical reactions occurred during this cathodic transformation. So a detailed mechanistic study seemed necessary to achieve large-scale selective synthesis of M-NH_2.

We report hereafter the results of this study concerning the electrochemical reduction of **1** and related streptogramin derivatives **2-10** (see Tables I, II and III). In addition, model compounds in which the peptidic lactone residue **M** had been replaced by aliphatic or aromatic groups were fruitfully used to investigate the effects of the peptidic lactone residue on the electrochemical behaviour of pyridyl carboxamides.

RESULTS AND DISCUSSION

Pristinamycin I_A (1) and related streptogramin derivatives (2-10)

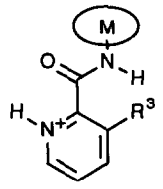
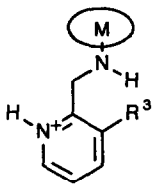
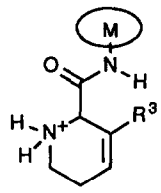
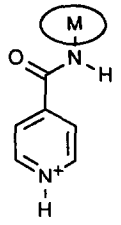
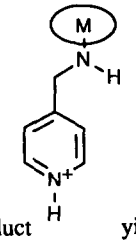
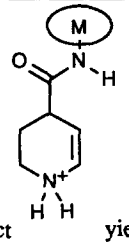
Compounds 1-5

A typical cyclic voltammogram of streptogramin derivatives **1-5** (Table I), in aqueous 0.5 mol.L^{-1} sulphuric acid solution, at a stationary mercury electrode, clearly showed two distinct reduction peaks Pc_1 and Pc_2, around -800 and -1000 mV s.c.e. respectively.

When the controlled-potential of the mercury pool working electrode (E) was fixed at -850 mV s.c.e., i.e. at a potential immediately following the first peak Pc_1 and preceding the second peak Pc_2, a coulometric value of 4.0 ± 0.2 was found for the number of electrons (n) involved in the reduction of one molecule of streptogramin derivatives **1-5**. As the electrolysis proceeded, a decrease in the first cathodic peak Pc_1 was observed and the voltammogram of the exhaustively reduced solution exhibited a sole cathodic peak at -1000 mV s.c.e.. Finally, preparative scale electrolyses allowed the isolation of two major compounds as indicated in Table I.

When E was fixed at -1000 mV s.c.e., i.e. at a potential corresponding to the second cathodic peak Pc_2, a coulometric value of 5.5 ± 0.2 was found for n; no cathodic peak was observed in the cyclic voltammogram of the exhaustively reduced solution of **1-5**. One or two major products were isolated after preparative scale electrolyses depending on the nature of the R^3 substituent (Table I).

Table I: Controlled potential (E) of the working mercury electrode, products and yields obtained from streptogramins 1-5.

 Compound R^3	E mV s.c.e.	22	 Product	yield	 Product	yield
1 OH	-850 -1000	15% (a) 50% (b)	23 –	35% –	– –	– –
2 OCH_3	-850 -1000	15% 45%	24 –	30% –	– 25	– 30%
3 F	-1000	30%	–	–	26	30%
4 H	-850 -1000	15% 80%	27 –	60% –	– –	– –
	E mV s.c.e.	 22	 Product	yield	 Product	yield
5	-850 -1000	15% 80%	28 –	60% –	– –	– –

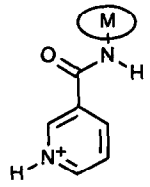
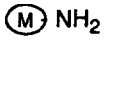
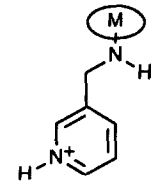
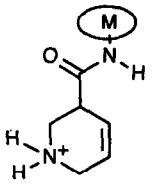
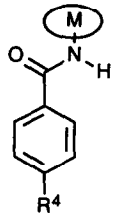
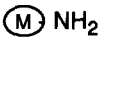
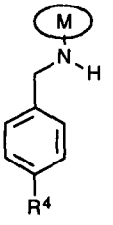
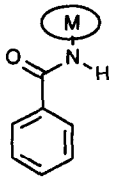
(a) beside M-NH_2, 3-hydroxypicolyl alcohol resulting from the C-N splitting reaction was isolated in about 10% yield.

(b) beside M-NH_2 and 3-hydroxypicolyl alcohol, 3-hydroxy-2-picoline was produced in about 20% yield.

Compounds 6-8

In the cyclic voltammogram of compounds **6-8**, no cathodic peak was recorded before the hydrogen evolution. For this reason, preparative scale electrolyses were conducted at the hydrogen ion discharge potential (-1150 mV s.c.e.). The results of our experiments are summarized in table II.

Table II: Products and yields of controlled potential electrolyses of streptogramins 6-8.

	 22	 Product	yield	 Product	yield
6	15%	**29** (a)	20%	–	–
 Compound R^4	 22	 Product	yield	 Product	yield
7 H	–	–	–	**7**	(b)
8 SO_2CH_3	–	–	–	**7**	60%

(a) in addition to the production of M-NH_2 **22** and aminomethylpyridine derivative **29**, the electrolysis mixture contained numerous by-products which were not identified.

(b) a quantitative yield of starting material was recovered.

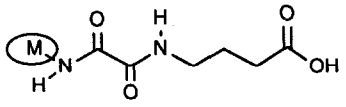
From these results, several points have to be underlined:

a) provided that E was fixed at -850 mV s.c.e., the presence of the peptidic lactone residue greatly favoured the formation of aminomethylpyridines **23**, **24**, **27** and **28**. Therefore, it could be deduced that this reductive electrochemical route was not specific to anilides, as previously reported in the heterocyclic carboxamide series[7]. Moreover, the yield of M-NH_2 **22** could be increased upon working at -1000 mV s.c.e., owing to the reduction of aminomethylpyridines **23**, **24**, **27** and **28** which produced the corresponding picoline and amine. The fact that picoline and amine were reliably formed from aminomethylpyridine was confirmed by a direct electrolysis of this compound performed at -1000 mV s.c.e., which yielded amine in quantitative yield. A similar cleavage reaction has been also reported in the course of the reduction of 4-anilinomethylpyridine[7].

b) likewise, isonicotinic amide **5** was reduced to aminomethylpyridine **28**, whereas the reduction of nicotinamide **6** was more difficult, and that of compound **7** impossible. Furthermore, introduction of the strong electron-withdrawing substituent SO_2CH_3 at the 4-position of the phenyl group (compound **8**) resulted in the cleavage of the C-S bond to produce compound **7** in 60% yield. Such reactions have been shown to occur with methyl-β-naphtylsulphone[25] and disulphones[26] in non-aqueous protic media. Due to the cathodic

limit of the solvent, the use of aqueous electrolytes makes this type of reaction usually difficult.

c) of particular interest was the unexpected production of tetrahydropyridine derivatives **25** and **26**, isolated in 30% yield (Table I), when compounds **2** (R^3= OCH_3) and **3** (R^3= F) were the starting materials. In contrast, when R^3= OH (pristinamycin I_A **1**), M-NH_2 was obtained in 50% yield and no tetrahydropyridine was detected. Moreover, in this case, a ring-opened by-product **30** was isolated in about 10% yield. No doubt this by-product resulted from a ring-cleavage of a two or four-electron reduction intermediate species. Then, an oxidative transformation, which cannot occur during the reductive electrolysis procedure, but in the course of the slightly basic aqueous work up, appears to be needed to go from **1** to the oxoamide **30**.



30

These results are original compared with those previously reported in the literature. In the case of pyridyl carboxamides, the isolation of partially reduced ring products was indeed considered by several authors to be limited to alkaline media[7,13,23]. Therefore, we focused our attention on this type of reaction and we decided to investigate the reduction of analogues **9** and **10** (Table III) containing respectively an isoquinoline and a 3-olate-pyridinium ring, both considered as electronic systems more easily reducible than the pyridine nucleus.

Compounds 9 and 10

In the cyclic voltammogram of compounds **9** and **10**, a sole cathodic peak Pc was recorded around -700 mV s.c.e.. With E being held more negative than E_{Pc}, a coulometric value of 2.5 to 4.0 ± 0.2 was found for n, depending on the selected potential. The results of the preparative electrolyses are collected in Table III.

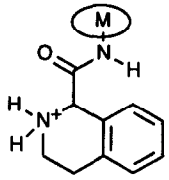
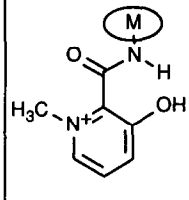
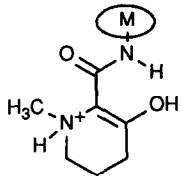
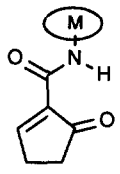
- When the electrolysis of **10** was carried out at -850 mV s.c.e., only compound **33** could be isolated in 10% yield. Its structure is consistent with the transient formation of an unstable dihydropyridine species, as already suggested in the case of **1** (see scheme 3).

- When working at -1000 mV s.c.e., tetrahydroisoquinoline **31** and tetrahydropyridine **32** were isolated in higher yields than those reported for tetrahydropyridines **25** and **26** (Table I), as could be expected from the following reducibility sequence: 3-methoxypyridinium ~ 3-fluoropyridinium < isoquinolinium ~ N-methylpyridinium.

At that point, a first conclusion could be drawn: compared with the results previously reported in the literature[4-13], the attachment of a peptidic lactone residue to the amide nitrogen markedly modified the behaviour of pyridyl carboxamides **1-10** in aqueous acidic medium. Firstly, it favoured the formation of the aminomethylpyridine derivatives and, secondly, it induced the formation of partially reduced ring products.

To clarify the role exerted by the peptidic lactone residue on the electrochemical reduction of streptogramin derivatives **1-10**, we then turned our attention to model compounds in which the peptidic lactone residue was absent and replaced by aliphatic or aromatic groups.

*Table III: Controlled potential (E), number of electrons (n), products and yields obtained from streptogramins **9** and **10**.*

	E mV s.c.e.	n	 **22**	 **31**	
	-700	2.3	33% (a)	–	
9	-850	3.0	26%	15%	
	-1000	4.6	15% (b)	45%	
	E mV s.c.e.	n	 **22**	 **32**	 **33**
	-850	2.5	–	–	10%
10	-1000	4.0	–	60%	–

(a) beside **M**-NH_2, 2-isoquinolyl alcohol resulting from the cleavage of the C-N bond was isolated in 30% yield.

(b) beside **M**-NH_2, 2-methyl-isoquinoline was detected instead of 2-isoquinolyl alcohol. At -1000 mV s.c.e., 2-isoquinolyl alcohol was indeed reductively cleaved to yield 2-methyl-isoquinoline, as confirmed by a direct electrolysis of 2-isoquinolyl alcohol under the same experimental conditions (see scheme 4).

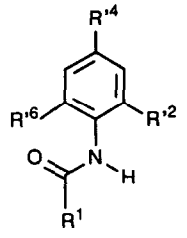
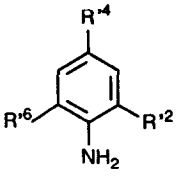
Model compounds (11-21)

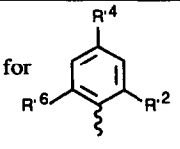
The results obtained with model compounds possessing an aliphatic chain instead of the peptidic lactone residue will not be detailed in this paper. The cathodic behaviour of these heterocyclic carboxamides, in which the amide nitrogen was substituted by an isobutyl or a 2-thiophenylethyl chain, was indeed similar to that previously reported in the literature[6-9]. In particular, isoquinoline or 3-olate-pyridinium derivatives did not yield partially reduced ring products in acidic medium. So, as expected from a steric standpoint, it is obvious that a R^2 aliphatic chain does not constitute a suitable model of macrolide **M**. Therefore, particular attention was devoted to the case of anilides (R^2= phenyl, compounds **11-19**).

Compounds 11-19 possessing an aromatic substituent R^2 at the nitrogen amide

A typical cyclic voltammogram of model compounds **11-19**, in aqueous sulphuric acid solution, at a stationary mercury electrode, showed a sole large cathodic peak in the potential range -600 to -850 mV s.c.e.. The results of the preparative scale electrolyses obtained when E was fixed at -1000 mV s.c.e. are collected in table IV.

*Table IV: Products and yields of controlled potential electrolyses of compounds **11-19**.*

 Compound	R^1	R'^2	R'^4	R'^6	 Product	yield	**Tetrahydroderivative*** Product	yield
11	1-methyl-3-olate-pyridinium-2-yl	H	H	H	–	–	**34**	60%
12	1-isoquinolyl	H	H	H	**35**	45%	**36**	27%
13	1-isoquinolyl	H	CN	H	**37**	40%	**38**	20%
14	1-isoquinolyl	H	OCH_3	H	**39**	50%	**40**	33%
15	1-isoquinolyl	CH_3	H	CH_3	**41**	10%	**42**	50%
16	1-isoquinolyl	$CH(CH_3)_2$	H	$CH(CH_3)_2$	–	–	**43**	75%
17	3-OCH_3-2-pyridyl	CH_3	H	CH_3	**41**	60%	–	–
18	3-OH-2-pyridyl	$CH(CH_3)_2$	H	$CH(CH_3)_2$	**44**	50%	–	–
19	3-OCH_3-2-pyridyl	$CH(CH_3)_2$	H	$CH(CH_3)_2$	**44**	50%	**45**	30%

* For structures **34** to **45**, see tables I and III substituting (M) for 

The effect of the substituents on the reduction of the pyridine or the isoquinoline ring can be assessed by comparing the yields of the tetrahydro compounds produced by the model compounds (Table IV) with those reported for the corresponding streptogramin tetrahydro derivatives (Table I and III). From this comparison, it is clear that betaines **10** and **11** behave similarly. On the basis of these findings, it would be reasonable to assume that the phenyl group constitutes an acceptable model for the peptidic lactone residue. However, this good concordance was no longer verified with the isoquinoline derivatives **9** and **12**, since the conversion of **12** into tetrahydroisoquinoline **36** (27%) was lower than the conversion of **9** into tetrahydroisoquinoline **31** (45%) (Table III). Consequently, to obtain a more accurate model of the macrolide, substituents of various stereoelectronic features were introduced onto the phenyl group as a means of modulating the two competitive pathways: cleavage of the C-N bond yielding the alcohol along with the substituted aniline and reduction of the heterocyclic nucleus into tetrahydro derivatives.

Data reported in table IV reveals that compounds **12, 13, 14** gave similar results: no significative change was observed when electron-withdrawing or -donating substituents were present at the 4-position of the phenyl group.

In contrast, the introduction of a bulky substituent (compounds **15** and **16**) promoted the reduction of the heterocyclic nucleus. In the case of the isoquinoline nucleus, the model compound **15** and the streptogramin derivative **9** gave similar results. Moreover, when comparing the results exhibited by the 3-methoxypyridyl carboxamides **17** and **19**, it appeared that 2,6-diisopropyl-phenyl group behaved as the most accurate model of the macrolide. Compound **19** afforded tetrahydropyridine **45** in similar yield to that obtained from the corresponding streptogramin derivative **2** (30%). Consistent with these results was the behaviour of model compound **18** which gave C-N bond cleavage reaction with the same overall yield (50%) as pristinamycin I_A **1**. Consequently, there was little doubt left that the steric hindrance exerted by the peptidic lactone residue accounted for the specific electrochemical behaviour of streptogramin derivatives **1-10**.

A last series of model compounds, in which the heterocyclic nucleus was replaced by a phenyl group, was finally investigated to assess the influence of the pyridyl ring on the reduction of the carboxamide.

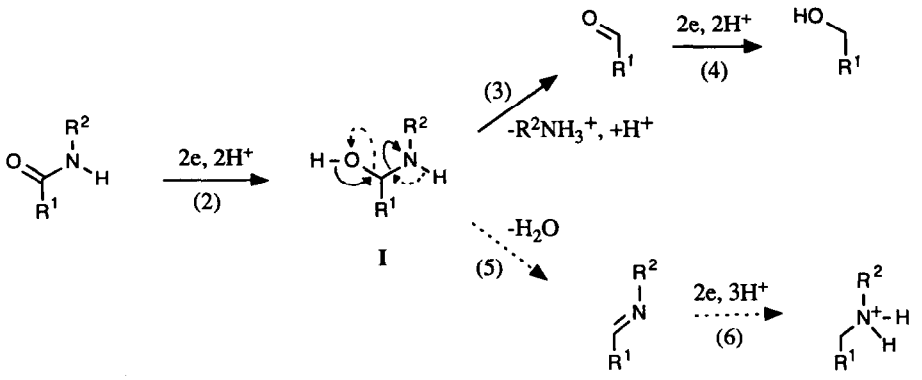
Compounds 20 and 21 possessing an aromatic substituent R^1

In the cyclic voltammogram of benzanilides C_6H_5-CO-NH-R^2 **20** (R^2 = C_6H_5) and **21** (R^2 = p-CN-C_6H_4), no peak was recorded before hydrogen evolution. For this reason, preparative scale electrolyses were conducted at the hydrogen ion discharge potential (-1150 mV s.c.e.). Only were isolated the corresponding benzylanilines C_6H_5-CH_2-NH-R^2 **46** (R^2 = C_6H_5) and **47** (R^2 = p-CN-C_6H_4), in respectively 20% and 60% yields (see experimental).

MECHANISTIC DEDUCTIONS

As mentioned in the introduction, many studies on the electrochemical reduction of carboxamides have been reported in the literature. Mainly based on the results obtained by H. Lund and co-workers[7-10], we can formulate the following assumptions about the mechanistic pattern of the pyridyl carboxamides reduction. As commonly admitted, both reduction of the CO group and cleavage of the C-N bond of amide would result

from the evolution of the hemiaminal key intermediate I[23] as shown in scheme 1.



Scheme 1

According to our results, only compounds **20** and **21** followed the dehydration route [eqn. (5)-(6)] to afford aminomethyl derivatives. This result may be explained by the intermediary formation of the conjugated C_6H_5-CH=N-C_6H_4-R'[4] moiety, following the involvement of two electrons in the reductive cleavage of the C-O bond. This reduction requires a more negative potential than that necessary to cleave the C-N bond [eqn. (3)], as demonstrated by the absence of any cathodic peak in the cyclic voltammogram, contrary to picolinamide which is reducible at about -800 mV s.c.e.

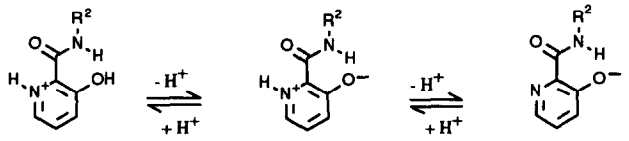
As no systematic study of the influence of electronic and steric factors on the ratio of C-N bond cleavage [eqn. (3)] versus dehydration [eqn. (5)] has been previously described in the literature, our experiments on pristinamycin I_A **1** and related streptogramins **2-10** were designed to study the mechanistic implications of such structural features. Beside these two competitive reactions, our results showed that the electrochemical reduction of streptogramins followed a third route featuring the production of partially reduced ring products, a reaction not yet reported in acidic media.

Though the first-formed intermediate species common to the three routes seems likely to be a 1,2-dihydro product, no direct evidence for the formation of the latter was obtained in our experiments. However, a number of factors arguing in favour of the formation of this key intermediate species could be listed. Indeed, when the electrolysis was carried out at -1000 mV s.c.e., tetrahydropyridines **25**, **26** (Table I), **32** (Table III), **34**, **45** (Table IV), and tetrahydroisoquinolines **31** (Table III), **36**, **38**, **40**, **42**, **43** (Table IV) were isolated in noticeable yields (20-75%), in consistence with the over- reduction of this 1,2-dihydro intermediate. Noteworthy was the specific behaviour of pristinamycin I_A **1** compared with that of related analogues **2** and **3**, all these compounds possessing a 3-substituted pyridine ring. Whereas **2** and **3** produced the tetrahydropyridines **25** and **26** respectively, in 30% yield each, it was not possible to isolate the tetrahydro product using **1** as starting material. To explain this last result, we assume that the key 1,2-dihydropyridyl intermediate is prone to ring opening as shown by the isolation of compound **30**.

In the case of pristinamycin I_A **1** and related streptogramin derivatives, the unusual formation in

aqueous acidic medium of partially reduced ring products is probably the consequence of steric effects. The steric hindrance generated by the R^2 group induces a severe decrease of the amidic resonance, and this increases the electron withdrawing ability of the amide. As a consequence, the pyridyl ring is more easily reduced. The values of $(pKa_2)_{app}$ found for **1** and **18**, compared with that of 3-hydroxy-picolinamide (as shown in table V) are fully consistent with this rationale and moreover corroborate our finding that, in the studied series, the 2,6-diisopropylphenyl group behaves as the most accurate model of the Macrolide.

Table V: $(pKa)_{app}$ values measured spectrometrically for the subsequent equilibria[27]:



Compound	R^2	$(pKa_2)_{app}$	$(pKa_1)_{app}$
3-OH-picolinamide	H	2.50	7.90
18	2,6-diisopropyl-phenyl	1.70	7.80
1	(M)	1.00	7.20

From these results, it can be deduced that the cathodic electrolysis of pristinamycin I_A **1**, related streptogramins **2-6**, **9** and **10** (tables I, II and III) and model compounds **11-19** (Table IV), proceeds by at least two of the three competing routes :

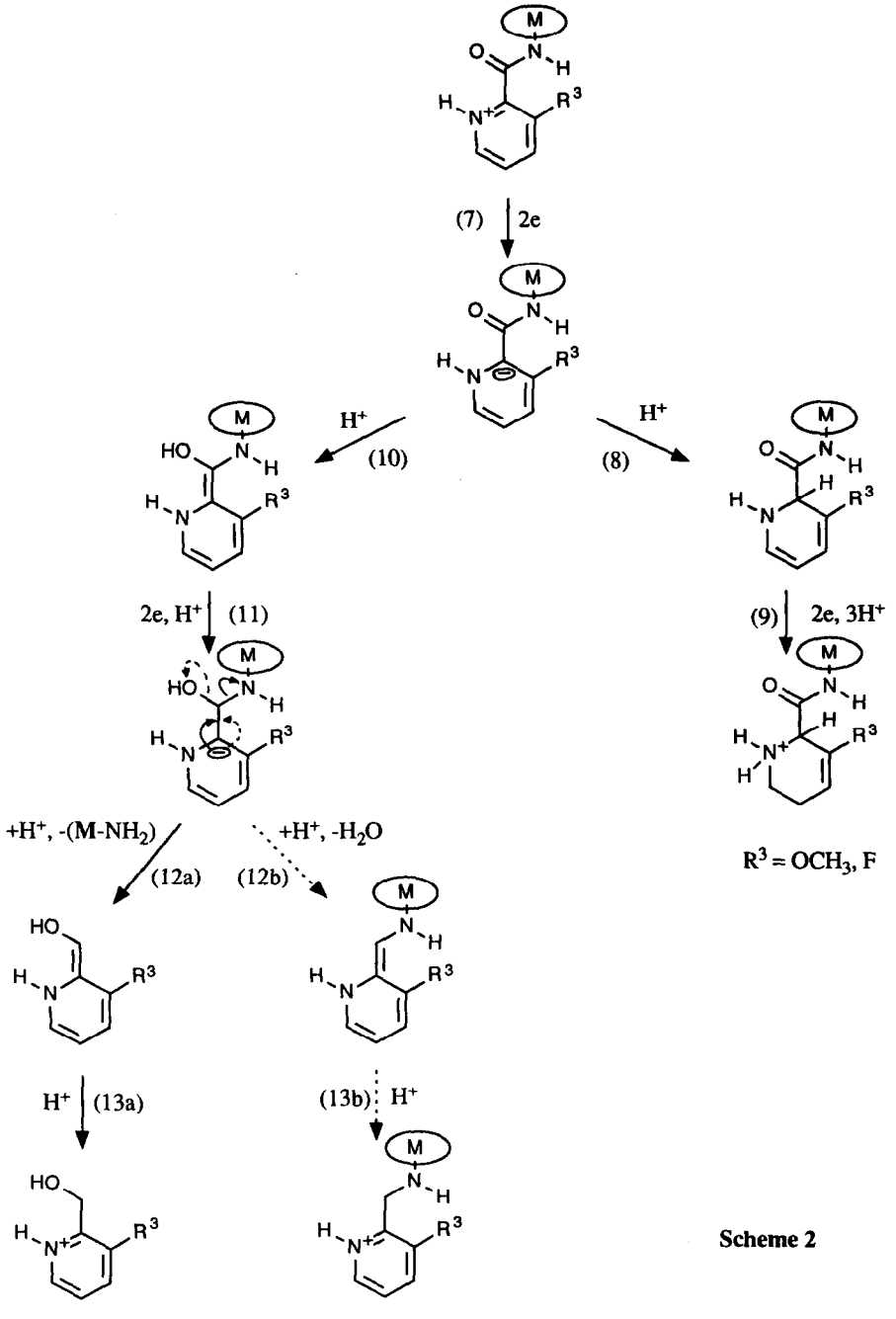
1- splitting of the C-N bond to yield an alcohol and the corresponding amine;

2- splitting of the C-O bond (dehydration) to give an aminomethylpyridine derivative;

3- reduction of the heterocyclic nucleus.

A tentative mechanism for the electrochemical reduction of pristinamycin I_A **1** and related streptogramins can be now proposed. The first two electrons required for the reduction are supposed to be delivered from the cathode to the heterocyclic ring. From this point, the key intermediate would be the transient carbanionic species formed at the C-2 position, after the consumption of two electrons per mole of substrate [eqn. (7)]. The subsequent step would consist either in a further two electron-reduction of the ring to afford the tetrahydro compounds [eqn. (8)-(9)] or in an intramolecular migration of the doublet of electrons from the reduced heterocyclic ring towards the side chain. This would result in the reductive cleavage of the

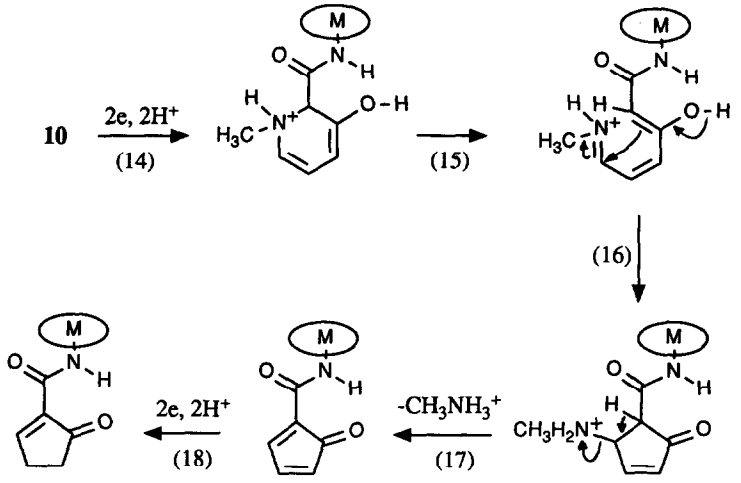
C-N or the C-O bonds to yield finally the alcohol [eqn. (10)-(13a)] or, alternatively, the aminomethylpyridine derivative [eqn. (10)-(13b)]. Thus, the driving force of the electron migration would be the tendancy to recover an aromatic system in the heterocyclic ring (scheme 2).



Scheme 2

The following observations are consistent with our hypothesis of competitive routes following the initial formation of a carbanion species at the C-2 position:

a) In the case of **10**, when the electrolysis was carried out at -850 mV s.c.e., the initial 1,2-dihydro product was subsequently transformed into a minor product **33** that was isolated in 10% yield. Its formation can be reasonably regarded as proceeding through a tandem electrocyclic ring opening-Mannich reaction, as shown in scheme 3.



Scheme 3

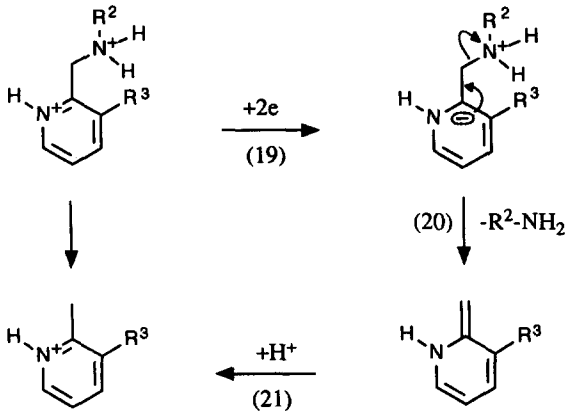
b) In the case of streptogramin **9**, the data collected in table III provide evidence for the influence of E on the competitive pathways. Increased value of E promoted cleavage of the C-N bond [via eqn. (12a)] at the expense of the heterocyclic ring reduction, so that, when E was less negative than -800 mV s.c.e., the reduction into tetrahydroisoquinoline derivative no longer occurred.

c) In the case of pyridyl carboxamides, as underlined earlier, the electrochemical behaviour depends on the position of the heterocyclic nitrogen atom. Picolinamide **4** and isonicotinamide **5** gave similar results (Table I). In contrast, when the formation of a carbanion at the C-2 position was no longer possible, as with nicotinamide **6**, the reduction seemed to be more difficult and occurred at the hydrogen evolution potential. In this case, the reducing agent could be $H^{\bullet}$.

d) With benzanilides **20** (R'^4 = H) and **21** (R'^4 = CN) which followed eqn. (5)-(6) in scheme 1, the yield in benzylanilines increased from 20% (**46**) to 60% (**47**) as a consequence of the higher withdrawing electron ability of the CN substituent compared to H. In contrast, with isoquinolyl derivatives **12-14**, the nature of R'^4 (OCH_3, H, CN) did not exert any influence on the cathodic behaviour, as could be expected if the reduction occurred at the heterocyclic nucleus, via a transient carbanionic species at the C-2 position. This hypothesis is again substantiated when considering analogue **7**, which possesses a phenyl ring instead of a 3-substituted pyridine ring as R^1 substituent. In this case, the aromatic nucleus was no longer reducible under our experimental conditions and none of the three possible competing routes was followed. The situation remained unchanged upon introduction of the SO_2CH_3 group at the 4-position of the phenyl group (compound **8**): as indicated earlier, only was observed the cleavage of the C-S bond (Table II). Therefore, in the series

studied, the presence of a strong withdrawing group within the R^1 substituent did not constitute the sole prerequisite to the amide group reducibility.

e) A last proof of the carbanion formation could be seen in the reduction of aminomethylpyridine (or isoquinolyl alcohol) which afforded 2-picoline (or 2-methyl-isoquinoline). This result could be explained by the evolution of the C-2 carbanion according to a route similar to eqn. 12a (or eqn. 12b) [see scheme 4]. Similarly, 2- and 4-methylpyridine were obtained from the corresponding hydroxymethylpyridines[28,29].



Scheme 4

When compared to previous results concerning the electrochemical reduction of pyridyl carboxamides, this work carried out on a series of streptogramin analogues highlighted the influence of the peptidic lactone residue at the amide nitrogen position. This influence was twofold : it favoured the production of aminomethylpyridine on the one hand, and that of tetrahydropyridine derivatives on the other hand. To the best of our knowledge, the formation of the latter by electrochemical reduction has not been reported previously in aqueous acidic medium: so far it has been considered as a general rule that the reduction of pyridinium ions bearing a reducible substituent led to the reduction of the latter, the isolation of partially-reduced ring products being limited to alkaline media[7,13].

Based upon a systematic structural change in a series of model compounds, we have demonstrated that increasing bulk at the amide nitrogen position led to higher amounts of tetrahydropyridine derivatives. We have also given evidence that the 2,6-diisopropylphenyl group behaved as the most accurate model of the peptidic lactone residue.

As a consequence of this work, the chemical deacylation of the pristinamycin I_A was finally achieved on large scale using zinc in hydrochloric acid[3] as a surrogate of the electrochemical reduction.

EXPERIMENTAL

Apparatus, cells and electrodes.

The ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AC 300 and AM 400 spectrometers operating at 300 and 400 MHz for ^1H observations. Chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane. The NMR abbreviations used are as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet; J, coupling constant. The protons noted prime are specific to those of the phenyl group. The measurements were carried out using the standard pulse sequences. The carbon type (methyl, methylene, methine or quaternary) was determined by DEPT experiments. Mass spectra were recorded on a Nermag R 10-10 C spectrometer equiped with electron impact (E.I.) and desorption chemical ionization (D.C.I.) modes. Samples were introduced by means of a direct insertion probe. Ammonia was used as the reagent gas. Infrared spectra were obtained in methanol (FMIR) on a FT spectrometer Nicolet 60 SXR. Melting points were determined on a Köfler block and were uncorrected.

Electrochemical measurements were made with a Tacussel PRG 5 multipurpose polarograph that was used only as a rapid-response potentiostat. For cyclic voltammetry, triangular waveforms were supplied by a Tacussel GSTP 4 function generator. Current-potential curves were recorded on a Sefram SI 8312 instrument. The cell was a Tacussel CPRA water-jacketed cell working at a temperature of 25°C. The reference electrode was an aqueous saturated calomel electrode (s.c.e.) (Tacussel C 10), to which all potentials quoted are referred. The counter electrode was a platinum Tacussel Pt 11. The working electrode was a Tacussel CMT 10/24 capillary. The aqueous or hydroalcoholic (50:50) sulfuric acid solutions (20 mL) of compounds **1-21** (0.04 mmol) were deaerated prior use by bubbling nitrogen through the solution for 15 min. Scanning started from -0.3 V s.c.e. towards -1.2 V s.c.e. and returned to -0.3 V s.c.e., at a rate of 0.2 Vs^{-1}.

Controlled potential electrolyses were carried out using a three compartment water jacketed cell. A Tacussel PJT 120-1 potentiostat and a Tacussel IG6-N electronic integrator were included in the circuit. The reference electrode has been mentioned above. The counter electrode was a platinum foil. The working electrode was a mercury pool (60 cm^2 area).

Chromatography

Analytical HPTLC and TLC were performed on Merck Silica Gel 60 F 254 (lots 5635 and 5714 respectively). Column chromatography was conducted on open glass columns packed with Merck Silica Gel 60 (lot 9385).

Materials

Pristinamycin I_A **1** was obtained from the bulk pharmaceutical and purified as described[2]. Streptogramins **2-10** were prepared[3] from **22** by standard methods[30]. The solvents used for extractions and chromatography were obtained from SDS. Methanol, sulphuric acid, sodium carbonate were obtained from Prolabo (analysis purity grade). 1-hydroxybenzotriazole, N-dimethylamino- propyl-N'-ethylcarbodiimide hydrochloride were obtained from Fluka. Substituted aromatic or heterocyclic (picolinic, 1-isoquinolyl...) acids, substituted anilines and benzanilide **20** were obtained from Aldrich.

The model compounds **11-19, 21** were synthesized as follows:

N-phenyl-(1-methyl-3-olate-pyridinium)-2-carboxamide 11

A solution of N-phenyl-3-hydroxy-picolinamide, synthesized using the method reported for compound

12 (see below), (2.00 g; 9.3 mmol) in 30 mL of dichloromethane: methanol (4:1), was stirred for 2 min at 10°C. A solution of diazomethane (0.46 g, 11 mmol) in ether (30 mL) was added dropwise. After addition, stirring was continued for 2h at 10°C, and for an additional 15h at room temperature. The reaction was quenched with 4 drops of concentrated acetic acid. The reaction mixture was poured into a 5% sodium hydrogenocarbonate aqueous solution (30 mL). The solvents were evaporated under reduced pressure to produce an aqueous solution that was saturated with sodium chloride and extracted with ethyl acetate (100 mL). The organic phase was dried over anhydrous sodium sulphate, and the solvent was removed under reduced pressure at 35°C.

Chromatography [dichloromethane:methanol (95:5)] afforded **11** as a yellow solid (1.40 g, 65% yield, mp, 150 ± 2°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.55 (s, 3H, CH_3), 7.10 [t, 1H, H(4'), J = 8 Hz], 7.20 [m, 2H, H(4) and H(5)], 7.35 [t, 2H, H(3') and H(5'), J = 8 Hz], 7.55 [dd, 1H, H(6), J = 8 Hz, J = 3 Hz], 7.70 [d, 2H, H(2') and H(6'), J = 8 Hz], 14.40 (s, 1H, NH, D_2O exchanged); ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.6 (CH_3), 120.8 [CH(2') and CH(6')], 124.1 [CH(4')], 125.7 [CH(5)], 128.7 [CH(3') and CH(5')], 130.1 [CH(4)], 130.5 (C-2), 138.4 (C-1'), 139.2 [CH(6)], 160.4 (C-3), 170.3 (CO, amide); MS (DCI): m/z = 229 (MH^+); elemental analysis: found (C, 68.38; H, 5.42; N, 12.41%), $C_{13}H_{12}N_2O_2$ requires (C, 68.42; H, 5.26; N, 12.28%).

N-phenyl isoquinoline-1-carboxamide 12

A reaction mixture of isoquinoline-1-carboxylic acid (1.00 g, 5.8 mmol), 1-hydroxy-benzotriazole (0.08 g, 0.6 mmol) and aniline (0.54 g, 5.8 mmol) in dichloromethane (50 mL) was stirred and cooled to 0°C in an ice-water bath. A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.22 g, 6.4 mmol) in dichloromethane (50 mL) was added dropwise. After addition, stirring was continued for 2h at 0°C, and for an additional 2h at 20°C. The reaction mixture was then evaporated to dryness under reduced pressure. The residue was poured into water (30 mL) and extracted with toluene (100 mL). The solvent was removed under reduced pressure at 35°C to produce an orange-coloured oil.

Chromatography (dichloromethane) afforded **12** as an amorphous solid (1.31 g, 91% yield, mp, 131 ± 2°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 [t, 1H, H(4'), J = 8 Hz], 7.40 [t, 2H, H(3') and H(5'), J = 8 Hz], 7.75 [m, 2H, H(6) and H(7)], 7.85 [m, 4H, H(2'), H(6'), H(4) and H(5)], 8.50 [d, 1H, H(3), J = 6 Hz], 9.75 [dd, 1H, H(8), J = 8 Hz, J = 2 Hz], 10.70 (s, 1H, NH, D_2O exchanged); ^{13}C NMR (75 MHz, $CDCl_3$): δ 119.7 [CH(2') and CH(6')], 124.2 [CH(4')], 124.8, 126.9, 127.7, 128.8, 130.5 [CH(4), CH(5), CH(6), CH(7) and CH(8)], 127.2 (Cq, isoquinoline), 129.0 [CH(3') and CH(5')], 137.5 (Cq, isoquinoline), 138.0 (C-1'), 139.8 [CH(3)], 147.4 (C-1), 163.6 (CO, amide); MS (DCI): m/z = 249 (MH^+); elemental analysis: found (C, 77.24; H, 5.02; N, 11.27%), $C_{16}H_{12}N_2O$ requires (C, 77.42; H, 4.84; N, 11.29%).

N-(4-cyano-phenyl)-isoquinoline-1-carboxamide 13

When applied to isoquinoline-1-carboxylic acid (1.00 g, 5.8 mmol) and 4-cyano-aniline (0.68 g, 5.8 mmol), the method above yielded a mixture of products.

Chromatography [toluene:acetone (98:2)] afforded **13** as an amorphous solid (0.48 g, 30% yield, mp, 202 ± 2°C) in addition to a noticeable amount of non reacted 4-cyano-aniline (50% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 [d, 2H, H(3') and H(5'), J = 9 Hz], 7.75 [m, 2H, H(5) and H(7)], 7.90 [m, 4H, H(2'), H(6'), H(4) and H(6)], 8.55 [d, 1H, H(3), J = 6 Hz], 9.65 [dd, 1H, H(8), J = 8Hz, J = 2Hz], 10.70 (s, 1H, NH, D_2O exchanged); ^{13}C NMR (75 MHz, $CDCl_3$): δ 107.0 (C-4'), 119.0 (CN), 119.5 [CH(2') and CH(6')], 125.5, 127.0, 127.3, 129.3, 130.8 [CH(4), CH(5), CH(6), CH(7) and CH(8)], 127.2 (Cq, isoquinoline), 133.3

[CH(3') and CH(5')], 137.6 (Cq, isoquinoline), 139.8 [CH(3)], 142.0 (C-1'), 146.2 (C-1), 163.8 (CO, amide); MS (DCI): m/z = 274 (MH^+); elemental analysis: found (C, 74.55; H, 4.29; N, 15.33%); $C_{17}H_{11}N_3O$ requires (C, 74.72; H, 4.03; N, 15.38%).

N-(4-methoxy-phenyl)-isoquinoline-1-carboxamide 14

The same method applied to isoquinoline-1-carboxylic acid (1.00 g, 5.8 mmol) and 4-methoxy-aniline (0.71 g, 5.8 mmol) yielded an orange-coloured oil.

Chromatography (dichloromethane) afforded **14** as an amorphous solid (1.22 g, 76% yield, mp, 130 ± 2°C); ^1H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H, OCH_3), 6.95 [d, 2H, H(3') and H(5'), J = 9 Hz], 7.70 [m, 4H, H(2'), H(6'), H(5) and H(7)], 7.85 [m, 2H, H(4) and H(6)], 8.50 [d, 1H, H(3), J = 6 Hz], 9.75 [dd, 1H, H(8), J = 6 Hz, J = 2 Hz], 10.20 (s, 1H, NH, D_2O exchanged); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5 (OCH_3), 114.2 [CH(3') and CH(5')], 121.5 [CH(2') and CH(6')], 124.7, 126.8, 127.8, 128.7, 130.5 [CH(4), CH(5), CH(6), CH(7) and CH(8)], 127.2 (Cq, isoquinoline), 131.2 (C-1'), 137.5 (Cq, isoquinoline), 140.0 [CH(3)], 147.6 (C-1), 156.3 (C-4'), 163.4 (CO, amide); MS (DCI): m/z = 279 (MH^+); elemental analysis: found (C, 73.00; H, 5.20; N, 9.85%), $C_{17}H_{14}N_2O_2$ requires (C, 73.38; H, 5.04; N, 10.07%).

N-(2,6-dimethyl-phenyl)-isoquinoline-1-carboxamide 15

The same method applied to isoquinoline-1-carboxylic acid (1.00 g, 5.8 mmol) and 2,6-dimethyl-aniline (0.70 g, 5.8 mmol) provided an orange solid.

Chromatography [dichloromethane:toluene (60:40)] afforded **15** as an amorphous solid (0.90 g, 57% yield, mp, 146 ± 2°C); ^1H NMR (300 MHz, $CDCl_3$): δ 2.35 [s, 6H, CH_3(2') and CH_3(6')], 7.15 [m, 3H, H(3'), H(4') and H(5')], 7.70 [m, 2H, H(5) and H(7)], 7.85 [m, 2H, H(4) and H(6)], 8.55 [d, 1H, H(3), J = 6 Hz], 9.65 [dd, 1H, H(8), J = 8 Hz, J = 2 Hz], 9.70 (s, 1H, NH, D_2O exchanged); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5 [CH_3(2') and CH_3(6')], 124.5 [CH(4')], 126.8, 127.0, 127.9, 128.7, 130.5 [CH(4), CH(5), CH(6), CH(7) and CH(8)], 127.2 (Cq, isoquinoline), 128.1 [CH(3') and CH(5')], 134.0 (C-1'), 135.5 (C-2' and C-6'), 137.5 (Cq, isoquinoline), 140.2 [CH(3)], 147.9 (C-1), 164.0 (CO, amide); MS(DCI): m/z = 277 (MH^+); elemental analysis: found (C, 77.85; H, 5.80; N, 10.03%), $C_{18}H_{16}N_2O$ requires (C, 78.26; H, 5.80; N, 10.14%).

N-(2,6-diisopropyl-phenyl)-isoquinoline-1-carboxamide 16

The same method applied to isoquinoline-1-carboxylic acid (1.00 g, 5.8 mmol) and 2,6-diisopropyl-aniline (1.03 g, 5.8 mmol) produced an orange solid.

Chromatography [light petroleum:dichloromethane (80:20)] provided **16** as an amorphous solid (0.77 g, 40% yield, mp, 133 ± 2°C) in addition to a noticeable amount of non-reacted 2,6-diisopropyl-aniline (30% yield); ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 [d, 12H, CH_3 (isopropyl), J = 6.5 Hz], 3.25 [septuplet, 2H, CH (isopropyl), J = 6.5 Hz], 7.25 [d, 2H, H(3') and H(5'), J = 8 Hz], 7.35 [m, 1H, H(4')], 7.70 [m, 2H, H(5) and H(7)], 7.85 [m, 2H, H(4) and H(6)], 8.55 [d, 1H, H(3), J = 6 Hz], 9.60 [m, 2H, H(8) and NH, (D_2O exchanged)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.7 (CH_3, isopropyl), 29.0 (CH, isopropyl), 123.4 [CH(3') and CH(5')], 124.5 [CH(4')], 127.3 (Cq, isoquinoline), 126.8, 128.0, 128.1, 128.8, and 130.5 [CH(4), CH(5), CH(6), CH(7) and CH(8)], 131.4 (C-1'), 137.5 (Cq, isoquinoline), 140.3 [CH(3)], 146.5 (C-2' and C-6'), 148.0 (C-1), 165.3 (CO, amide); MS (DCI): m/z = 333 (MH^+); elemental analysis: found (C, 79.00; H, 7.23; N, 8.35%); $C_{22}H_{24}N_2O$ requires (C, 79.52; H, 7.23; N, 8.43%).

N-(2,6-dimethyl-phenyl)-3-methoxy-picolinamide 17

A solution of N-(2,6-dimethyl-phenyl)-3-hydroxy-picolinamide, synthesized using the method above, (2.00 g, 7.8 mmol) and sodium methoxide (0.42 g, 7.8 mmol) in N,N-dimethylformamide (6 mL), was stirred for 2 min, at room temperature, under nitrogen. Dimethyl sulphate (1.00 g, 7.8 mmol) was added, and stirring was continued for 24h. Then, the resulting solution was poured into water (120 mL) and extracted with ethyl acetate (100 mL). The organic phase was washed vigorously with water and dried over anhydrous sodium sulphate, and the solvent was removed under reduced pressure at 35°C.

After chromatography [toluene:acetone (85:15)] **17** was recovered as an amorphous solid (0.76 g, 38% yield, mp, 136 ± 2°C) in addition to a noticeable amount of non reacted material (20% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 [s, 6H, CH_3(2') and CH_3(6')], 3.95 (s, 3H, OCH_3), 7.10 [m, 3H, H(3'), H(4') and H(5')], 7.45 [m, 2H, H(4) and H(5)], 8.25 [dd, 1H, H(6), J = 4.0 Hz, J = 1.5 Hz], 9.10 (s, 1H, NH, D_2O exchanged); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5 (CH_3), 56.0 (OCH_3), 120.7, 126.8, 127.1 [CH(4'), CH(4), and CH(5)], 127.9 [CH(3') and CH(5')], 134.0 (C-1'), 135.4 (C-2' and C-6'), 138.5 (C-2), 140.1 [CH(6)], 156.1 (C-3), 162.1 (CO, amide); MS (DCI): m/z = 257 (MH^+); elemental analysis: found (C, 70.25; H, 6.39; N, 10.94%), $C_{15}H_{16}N_2O_2$ requires (C, 70.31; H, 6.25; N, 10.94%).

N-(2,6-diisopropyl-phenyl)-3-hydroxy-picolinamide 18

The method of preparation of compound **12**, when applied to 3-hydroxy-picolinic acid (2.10 g, 15 mmol) and 2,6-diisopropyl-aniline (2.65 g, 15 mmol), afforded **18** after chromatography [toluene:acetone (98:2)] as an amorphous solid (3.80 g, 85% yield, mp, 86 ± 2°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 [d, 12H, CH_3 (isopropyl), J = 6.0 Hz], 3.10 [septuplet, 2H, CH (isopropyl), J = 6.0 Hz], 7.25 [d, 2H, H(3') and H(5'), J = 8.0 Hz], 7.35 [m, 3H, H(4'), H(4) and H(5)], 8.15 [dd, 1H, H(6), J = 4.0 Hz, J = 1.5 Hz], 9.35 (s, 1H, NH, D_2O exchanged), 12.10 (s, 1H, OH, D_2O exchanged); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6 (CH_3, isopropyl), 29.0 (CH, isopropyl), 123.6 [CH(3') and CH(5')], 126.3, 128.7, 128.9 [CH(4'), CH(4) and CH(5)], 129.8 (C-1'), 131.2 (C-2), 139.7 [CH(6)], 146.2 (C-2' and C-6'), 158.2 (C-3), 168.4 (CO, amide); MS (DCI): m/z = 299 (MH^+); elemental analysis: found (C, 73.05; H, 7.82; N, 9.18%), $C_{18}H_{22}N_2O_2$ requires (C, 72.48; H, 7.38; N, 9.39%).

N-(2,6-diisopropyl-phenyl)-3-methoxy-picolinamide 19

Compound **19** was synthesized from **18** (2.32 g, 7.8 mmol) and dimethyl sulphate (1.00 g, 7.8 mmol) as described for **17**.

Chromatography [toluene:acetone (85:15)] afforded compound **19** as an amorphous solid (0.85 g, 35% yield, mp, 108 ± 2°C) along with a noticeable amount of starting material (20% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 [d, 12H, CH_3 (isopropyl), J = 6.0 Hz], 3.20 [septuplet, 2H, CH (isopropyl), J = 6.0 Hz], 3.95 (s, 3H, OCH_3), 7.20 [d, 2H, H(3') and H(5'), J = 8 Hz], 7.30 [t, 1H, H(4'), J = 8 Hz], 7.45 [m, 2H, H(4) and H(5)], 8.30 [dd, 1H, H(6), J = 4.0 Hz, J = 1.5 Hz], 9.10 (s, 1H, NH, D_2O exchanged); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6 (CH_3, isopropyl), 28.7 (CH, isopropyl), 56.1 (OCH_3), 123.2 [CH(3') and CH(5')], 120.7, 127.1 and 127.9 [CH(4'), CH(5) and CH(5)], 131.5 (C-1'), 138.8 (C-2), 140.3 [CH(6)], 146.2 (C-2' and C-6'), 156.0 (C-3), 163.1 (CO, amide); MS (DCI): m/z = 313 (MH^+); elemental analysis: found (C, 72.92; H, 7.72; N, 8.97%), $C_{19}H_{24}N_2O_2$ requires (C, 73.08; H, 7.69; N, 8.97%).

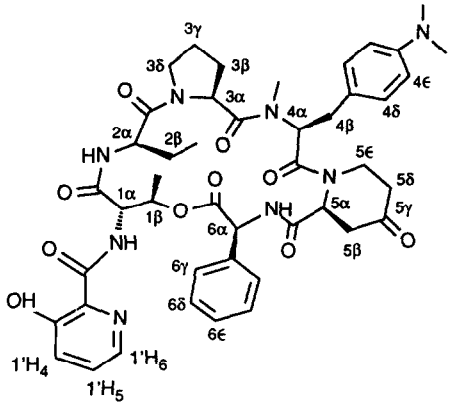
N-(4-cyano-phenyl)-benzamide 21

The method of preparation of compound **12** when applied to benzoic acid (1.22 g, 10 mmol) and 4-cyano-aniline (1.18 g, 10 mmol) yielded a mixture of products.

After chromatography [toluene:dichloromethane (85:15)], **21** was isolated as an amorphous solid (0.67 g, 30% yield, mp, 167 ± 2°C) along with a noticeable amount of non reacted 4-cyano-aniline (60% yield); ^{1}H NMR (300 MHz, DMSO D^6): δ 7.60 [m, 3H, H(3), H(4) and H(5)], 7.80 [d, 2H, H(3') and H(5'), J = 8 Hz], 8.00 [m, 4H, H(2), H(6), H(2') and H(6')], 10.60 (s, 1H, NH, D_2O exchanged); ^{13}C NMR (75 MHz, $CDCl_3$): δ 106.4 (C-4'), 120.2 (CN), 121.2 [CH(2') and CH(6')], 128.9 [CH(3) and CH(5)], 129.5 [CH(2) and CH(6)], 133.0 [CH(4)], 134.2 [CH(3') and CH(5')], 135.5 (C-1), 144.0 (C-1'), 167.3 (CO, amide); MS (DCI): m/z = 223 (MH^+); elemental analysis: found (C, 75.20; H, 4.86; N, 12.75%), $C_{14}H_{10}N_2O$ requires (C, 75.67; H, 4.50; N, 12.61%).

Isolation and spectroscopic data of products 22-47

The atoms of pristinamycin I_A are numbered as indicated below[31].



1-des-(3-hydroxy-picolinoyl)-pristinamycin I_A 22 and aminomethylpyridine 23

Method A: 200 mL of an aqueous sulphuric acid (0.5 mol.L^{-1}) solution of pristinamycin I_A **1** (346 mg, 0.4 mmol) were reduced under nitrogen, at 25°C, at a mercury pool working electrode (E = -850 mV s.c.e.). After exhaustive electrolysis, i.e., when a steady state minimum value of the current was recorded, the resulting solution was neutralized by a sodium carbonate solution (5 mol.L^{-1}) and extracted with dichloromethane (200 mL). The organic phase was dried over anhydrous sodium sulphate and the solvent removed under reduced pressure at 30°C. Chromatography [dichloromethane:methanol (98:2)] afforded compounds **22** (45 mg, 15% yield, mp, 206 ± 2°C), and **23** (120 mg, 35% yield, decomposes above 170°C) as amorphous solids.

1-des-(3-hydroxypicolinoyl)-pristinamycin I_A 22: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.35 (dd, 1H, $5\beta_2$), 0.91 (t, 3H, 2γ), 1.10 to 1.30 (m, 2H, $3\gamma_2$ and $3\beta_2$), 1.38 (d, 3H, 1γ), 1.52 (m, 1H, $3\gamma_1$), 1.65 to 1.80 (m, 2H, $2\beta_1$ and $2\beta_2$), 2.02 (m, 1H, $3\beta_1$), 2.10 to 2.35 (m, 3H, $5\delta_1$, $5\delta_2$ and $5\beta_1$), 2.74 (dt, 1H, $5\epsilon_2$), 2.87 [s, 6H, $N(CH_3)_2$], 2.98 (dd, 1H, $4\beta_2$), 3.30 (s, 3H, NCH_3), 3.20 to 3.40 (m, 3H, $3\delta_2$, $4\beta_1$ and 1α), 3.52 (m, 1H, $3\delta_1$), 4.60 to 4.90 (m, 3H, 3α, $5\epsilon_1$ and 2α), 4.97 (d, 1H, 5α), 5.24 (dd, 1H, 4α), 5.75 (broad q, 1H, 1β), 5.83 (d, 1H, 6α), 6.63 (d, 2H,

4ε), 7.10 to 7.35 [m, 7H, 4δ and aromatic (6)], 8.00 (d, 1H, 2NH, D_2O exchanged), 8.63 (d, 1H, 6NH, D_2O exchanged); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.8 (2γ), 17.8 (1γ), 25.0 (3γ), 26.0 (2β), 28.5 (3β), 32.0 (NCH_3), 36.5 (4β), 37.5 (5β), 39.8 (5δ), 41.5 [$N(CH_3)_2$], 42.0 (5ε), 48.2 (3δ), 51.7 (5α), 55.0 (2α), 57.0 (4α), 57.6 (3α), 58.0 (1α), 59.0 (6α), 72.8 (1β), 113.5 (4ε), 123.0 (4γ), 128.0 (4δ), 128.5, 129.0, 131.0 [CH, aromatic (6)], 137.5 [Cq, aromatic (6)], 151.0 [Cq-$N(CH_3)_2$], 169.0, 169.2, 171.0, 171.3, 172.0, 173.0 (CO, amides and ester), 204.5 (5γ); MS (DCI): m/z = 746 (MH^+).

1-des-(3-hydroxy-picolinoyl)-1-[2-(3-hydroxy-pyridyl)]-methyl-pristinamycin I_A 23: ^1H NMR (400 MHz, $CDCl_3$): δ 0.00 (dd, 1H, $5\beta_2$), 0.91 (t, 3H, 2γ), 1.10 to 1.40 (m, 2H, $3\gamma_2$ and $3\beta_2$), 1.50 (d, 3H, 1γ), 1.60 to 1.90 (m, 3H, $3\gamma_1$, $2\beta_1$ and $2\beta_2$), 2.00 to 2.20 (m, 4H, $5\beta_1$, $5\delta_1$, $5\delta_2$ and $3\beta_1$), 2.70 (dt, 1H, 5 ϵ_2), 2.80 [s, 6H, $N(CH_3)_2$], 2.90 (dd, 1H, $4\beta_2$), 3.20 (m, 1H, $4\beta_1$), 3.30 (s, 3H, NCH_3), 3.60 to 3.80 (m, 3H, 1α, $3\delta_1$ and $3\delta_2$), 3.90 to 4.10 (dd, 2H, 1'$\underline{CH_2}$-NH), 4.50 to 4.60 (m, 2H, $5\epsilon_1$ and 3α), 4.70 (d, 1H, 5α), 4.90 (q, 1H, 2α), 5.10 (dd, 1H, 4α), 5.80 (m, 2H, 1β and 6α), 6.35 (d, 2H, 4ε), 6.70 (d, 2H, 4δ), 7.30 [m, 6H, 1'H_5 and aromatic (6)], 7.40 (dd, 1H, 1'H_4), 8.00 (d, 1H, 2NH, D_2O exchanged), 8.25 (dd, 1H, 1'H_6), 8.75 (d, 1H, 6NH, D_2O exchanged). ^{13}C NMR (100 MHz, $CDCL_3$): δ 10.5 (2γ), 17.0 (1γ), 25.2 (3γ), 25.4 (2β), 28.6 (3β), 32.0 (NCH_3), 36.2 (4β), 37.5 (5β), 39.5 (5δ), 41.5 [$N(CH_3)_2$ and 5ε], 46.5 (1'$\underline{CH_2}$-NH), 49.0 (3δ), 52.0 (5α), 55.0 (2α), 57.0 (3α), 57.5 (6α), 58.5 (4α), 63.0 (1α), 72.8 (1β), 113.0 (4ε), 123.0 (4γ), 128.5 (4δ), 128.0, 129.0, 131.0 [CH, aromatic (6)], 137.0 [Cq, aromatic (6)], 151.0 [Cq-$N(CH_3)_2$], 168.0, 169.0, 170.0, 171.4, 171.5, 172.2 (CO, amides and ester), 204.2 (5γ); MS (DCI): m/z = 853 (MH^+).

Using method A, but working at - 1000 mV s.c.e., preparative scale electrolysis of **1** afforded, after chromatography, **22** (150 mg, 50% yield) along with a minor by-product **30** (36 mg, 10% yield).

***[4-[1-des-(3-hydroxy-picolinoyl)-pristinamycin I_A 1-oxalyl]-amino]-butyric acid* 30**: ^1H NMR (400 MHz, $CDCl_3$ + CD_3COOD): δ 0.60 (dd, 1H, $5\beta_2$), 0.85 (m, 4H, 2γ and $3\beta_2$), 1.25 (d, 3H, 1γ), 1.35 (m, 1H, $3\gamma_2$), 1.50 to 1.80 (m, 3H, $3\gamma_1$, $2\beta_1$ and $2\beta_2$), 2.00 [m, 4H, $3\beta_1$, $5\delta_2$ and CH_2], 2.25 (m, 2H, $5\beta_1$ and $5\delta_1$), 2.45 [m, 2H, $CH_2(CO)$], 2.75 (dt, 1H, $5\epsilon_2$), 2.85 [s, 6H, $N(CH_3)_2$], 3.00 (dd, 1H, $4\beta_2$), 3.30 (m, 4H, $4\beta_1$ and NCH_3), 3.50 [m, 3H, $3\delta_2$ and CH_2N], 3.65 (m, 1H, $3\delta_1$), 4.55 (t, 1H, 3α), 4.65 (m, 1H, $5\epsilon_1$), 4.75 (s, 1H, 1α), 4.85 (q, 1H, 2α), 5.40 (d, 1H, 5α), 5.60 (dd, 1H, 4α), 5.75 (m, 2H, 6α and 1β), 6.70 (d, 2H, 4ε), 7.20 [m, 8H, 4δ and aromatic (6)], 7.55 (d, 1H, 2NH, D_2O exchanged), 7.90 (d, 1H, 1NH, D_2O exchanged), 8.15 [t, 1H, CO$\underline{N}$H-CH_2N, D_2O exchanged], 8.50 (d, 1H, 6NH, D_2O exchanged); MS (DCI): m/z = 903 (MH^+); IR ν_{max} cm^{-1}: 2930 (CH_2), 1675 (CO, oxamide), 1625 (CO, CO_2^-), 1500 (NH, oxamide), 1415 (CO, CO_2^-).

Method B: 200 mL of an hydroalcoholic (50:50) sulphuric acid solution (0.5 $mol.L^{-1}$) of aminomethyl pyridine **23** (341 mg, 0.4 mmol) were reduced, under nitrogen, at 25°C, at a mercury pool working electrode (E = -1000 mV s.c.e.). After exhaustive electrolysis, the hydroalcoholic solution was concentrated to 100 mL under reduced pressure at 40°C. The resulting solution was neutralized by a sodium carbonate solution (5 $mol.L^{-1}$) and extracted with dichloromethane (200 mL). The organic phase was dried over anhydrous sodium sulphate and the solvent removed under reduced pressure at 30°C. Chromatography (dichloromethane:methanol (98:2)] permitted the isolation of compound **22** (270 mg, 90% yield).

1-des-(3-hydroxy-picolinoyl)-1-[2-(3-methoxy-pyridyl)]-methyl-pristinamycin I_A 24

Method A applied to **2** (352 mg, 0.4 mmol) afforded compound **24** as an amorphous solid (104 mg, 30% yield, decomposes above 165°C) along with **22** (15% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 0.10 (dd, 1H,

$5\beta_2$), 0.85 (t, 3H, 2γ), 1.30 (d,3H, 1γ), 1.35 (m, 2H, $3\gamma_2$ and $3\beta_2$), 1.50 to 1.90 (m, 3H, $3\gamma_1$, $2\beta_1$ and $2\beta_2$), 2.00 to 2.20 [m, 4H, $3\beta_1$, $5\beta_1$, $5\delta_1$ and $5\delta_2$), 2.65 (dt, 1H, $5\epsilon_2$), 2.85 [s, 6H, $N(CH_3)_2$], 2.95 (dd, 1H, $4\beta_2$), 3.25 [m, 5H, 1α, $4\beta_1$ and NCH_3], 3.30 to 3.60 (m, 2H, $3\delta_1$ and $3\delta_2$), 3.90 (s, 3H, OCH_3), 4.00 to 4.20 (dd, 2H, 1'$\underline{CH_2}$-NH), 4.60 (m, 2H, 3α and $5\epsilon_1$), 4.75 (q, 1H, 2α), 5.10 (d, 1H, 5α), 5.25 (dd, 1H, 4α), 5.60 (m, 1H, 1β), 5.80 (d, 1H, 6α), 6.55 (d, 2H, 4ϵ), 7.05 (d, 2H, 4δ), 7.10 to 7.30 [m, 7H, 1'H_4, 1'H_5 and aromatic (6)], 8.15 (dd, 1H, 1'H_6), 8.30 (d, 1H, 2NH, D_2O exchanged), 8.50 [d, 1H, 6NH, D_2O exchanged]; MS (DCI): m/z = 867 (MH^+).

1-des-(3-hydroxy-picolinoyl)-1-(3-methoxy-1,2,5,6-tetrahydropicolinoyl)-pristinamycin I_A 25

When the potential was fixed at -1000 mV s.c.e., method A applied to **2** (352 mg, 0.4 mmol) afforded compound **22** (45% yield) and compound **25** (106 mg, 30% yield, mp, 185 ± 2°C) as a mixture of two isomers A and B that could be separated.

Isomer A (17% yield): ^1H NMR (400 MHz, $CDCl_3$): δ 0.40 (dd, 1H, $5\beta_2$), 0.95 (t, 3H, 2γ), 1.20 (m, 1H, $3\beta_2$), 1.30 (d, 3H, 1γ), 1.40 (m, 1H, $3\gamma_2$), 1.60 to 1.80 (m, 3H, $2\beta_1$, $2\beta_2$ and $3\gamma_1$), 2.15 (m, 1H, $3\beta_1$), 2.20 to 2.40 [m, 5H, $5\beta_1$, $5\delta_1$, $5\delta_2$ and 1'CH_2(5)], 2.80 (dt, 1H, $5\epsilon_2$), 2.90 [s, 6H, $N(CH_3)_2$], 2.90 to 3.20 (m, 2H, $4\beta_2$ and 1'CH_2(6)], 3.30 [m, 4H, $4\beta_1$ and NCH_3], 3.45 (m, 1H, $3\delta_2$), 3.60 (m, 1H, $3\delta_1$), 3.75 (s, 3H, OCH_3), 4.20 (s, 1H, 1'H_2), 4.55 (t, 1H, 3α), 4.70 (m, 1H, $5\epsilon_1$), 4.85 (q, 1H, 2α), 4.95 (d, 1H, 1α), 5.05 (t, 1H, 1'H_4), 5.10 (d, 1H, 5α), 5.40 (dd, 1H, 4α), 5.90 (m, 2H, 1β and 6α), 6.65 (d, 2H, 4ϵ), 7.20 to 7.40 [m, 7H, 2NH and aromatic (6)], 7.90 (d, 1H, 1NH), 8.65 (d, 1H, 6NH); MS (DCI): m/z = 885 (MH^+).

Isomer B (13% yield): ^1H NMR (400 MHz, $CDCl_3$): δ 0.30 (dd, 1H, $5\beta_2$), 2.05 (m, 1H, $3\beta_1$), 3.60 (s, 3H, OCH_3), 4.05 (s, 1H, 1'H_2), 4.80 (d, 1H, 1α), 5.00 (d, 1H, 5α), 5.80 (q, 1H, 1β); MS (DCI): m/z = 885 (MH^+).

1-des-(3-hydroxy-picolinoyl)-1-(3-fluoro-1,2,5,6-tetrahydropicolinoyl)-pristinamycin I_A 26

When the potential was fixed at -1000 mV s.c.e., method A applied to **3** (347 mg, 0.4 mmol) afforded **26** (105 mg, 30% yield) as an amorphous solid along with compound **22** (30% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 0.35 (dd, 1H, $5\beta_2$), 0.95 (t, 3H, 2γ), 1.10 (m, 1H, $3\beta_2$), 1.20 to 1.40 (m, 4H, $3\gamma_2$ and 1γ), 1.50 to 1.80 (m, 3H, $2\beta_1$, $2\beta_2$ and $3\gamma_1$), 2.05 (m, 1H, $3\beta_1$), 2.10 to 2.40 [m, 5H, $5\beta_1$, $5\delta_1$, $5\delta_2$ and 1'CH_2(5)], 2.85 (dt, 1H, $5\epsilon_2$), 2.90 [s, 6H, $N(CH_3)_2$], 2.90 to 3.10 [m, 3H, 1'CH_2(6), $4\beta_2$], 3.20 to 3.40 [m, 5H, $4\beta_1$, $3\delta_2$ and NCH_3], 3.55 (m, 1H, $3\delta_1$), 4.30 (bs, 1H, 1'H_2, J_{HF} = 3 Hz), 4.60 (t, 1H, 3α), 4.75 (m, 1H, $5\epsilon_1$), 4.85 (q, 1H, 2α), 4.95 (d, 1H, 1α), 5.05 (d, 1H, 5α), 5.45 (dd, 1H, 4α), 5.60 (ddd, 1H, 1'H_4, J_{HF} = 18 Hz), 5.85 (m, 1H, 1β), 5.90 (d, 1H, 6α), 6.60 (d, 2H, 4ϵ), 6.70 (d, 1H, 2NH, D_2O exchanged), 6.95 (dd, 1H, 1NH, D_2O exchanged), 7.10 (d, 2H, 4δ), 7.15 to 7.40 [m, 6H, aromatic (6)], 8.55 (d, 1H, 6NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0 (2γ), 17.0 (1γ), 24.3 [1'CH_2(5)], 25.3 (3γ), 25.5 (2β), 28.5 (3β), 32.0 (NCH_3), 36.8 (4β), 38.0 (5ϵ), 40.0 (5δ), 40.8 [1'CH_2(6)], 41.5 [$N(CH_3)_2$], 41.7 (5β), 48.5 (3δ), 52.2 (2α), 54.3 (4α), 56.5 (1α and 6α), 57.0 [d, 1'CH(2), J_{CF} = 25 Hz], 57.5 (5α), 58.2 (3α), 72.0 (1β), 105.5 [d, 1'CH(4), J_{CF} = 10 Hz], 113.5 (4ϵ), 123.0 (4γ), 128.0, 129.0, 129.5 [CH, aromatic (6)], 131.0 (4δ), 137.0 [Cq, (aromatic (6)], 151.0 [Cq-$N(CH_3)_2$], 155.0 (d, 1'C-3, J_{CF} = 250 Hz), 168.5, 168.6, 169.0, 171.0, 171.2, 172.0, 173.0 (CO, amides and ester), 205.0 (5γ). MS (DCI): m/z = 873 (MH^+).

1-des-(3-hydroxy-picolinoyl)-1-(2-pyridyl)-methyl-pristinamycin I_A 27

Method A applied to **4** (340 mg, 0.4 mmol) afforded aminomethylpyridine **27** as an amorphous solid (200 mg, 60% yield, decomposes above 150°C) along with compound **22** (15% yield). ^1H NMR (400 MHz,

$CDCl_3$): δ 0.10 (dd, 1H, $5\beta_2$), 0.91 (t, 3H, 2γ), 1.10 to 1.40 (m, 2H, $3\gamma_2$ and $3\beta_2$), 1.45 (d, 3H, 1γ), 1.50 to 1.90 (m, 4H, $3\gamma_1$, $2\beta_1$, $2\beta_2$ and $3\beta_1$), 1.90 to 2.20 (m, 3H, $5\beta_1$, $5\delta_1$ and $5\delta_2$), 2.50 (broad s, 1H, 1'NH, D_2O exchanged), 2.70 (dt, 1H, $5\epsilon_1$), 2.80 [m, 7H, $4\beta_2$ and $N(CH_3)_2$], 3.30 (m, 4H, NCH_3 and $4\beta_1$), 3.40 (d, 1H, 1α), 3.50 (m, 2H, $3\delta_1$ and $3\delta_2$), 4.00 (m, 2H, 1'$\underline{CH_2}$-NH), 4.60 (m, 2H, $5\epsilon_1$ and 3α), 4.80 (m, 2H, 2α and 5α), 5.05 (dd, 1H, 4α), 5.80 (m, 2H, 6α and 1β), 6.40 (d, 2H, 4ϵ), 6.70 (d, 2H, 4δ), 7.20 [m, 7H, 1'H_5 and aromatic (6)], 7.50 (d, 1H, 1'H_3), 7.80 (dt, 1H, 1'H_4), 8.05 (d, 1H, 2NH, D_2O exchanged), 8.65 (dd, 1H, 1'H_6), 8.70 (d, 1H, 6NH, D_2O exchanged). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.1 (2γ), 17.1 (1γ), 24.5 (2β), 25.3 (3γ), 27.9 (3β), 31.1 (NCH_3), 35.8 (4β), 37.0 (5β), 39.0 (5δ), 40.6 [$N(CH_3)_2$], 40.9 (5ϵ), 47.8 (3δ), 51.0 (1α), 52.7 (1'$\underline{CH_2}$-NH), 54.2 (2α), 56.3 (3α), 57.0 (4α), 57.5 (5α), 63.3 (6α), 72.5 (1β), 112.8 (4ϵ), 122.3 (4γ), 122.6 and 123.0 (1'H_5 and 1'H_3), 127.8, 128.0, 128.5 [CH, aromatic (6)], 130.2 (4δ), 136.8 [Cq, aromatic (6)], 137.2 (1'H_4), 149.6 [Cq-$N(CH_3)_2$], 150.3 (1'H_6), 159.2 (1'Cq), 168.5 to 172.3 (CO, amides and ester), 204.0 (5γ); MS (DCI): m/z = 837 (MH^+).

1-des-(3-hydroxy-picolinoyl)-1-(4-pyridyl)-methyl-pristinamycin I_A 28

Method A applied to **5** (340 mg, 0.4 mmol) afforded aminomethylpyridine **28** as an amorphous solid (200 mg, 60% yield, decomposes above 150°C) along with compound **22** (15% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 0.00 (dd, 1H, $5\beta_2$), 0.95 (t, 3H, 2γ), 1.20 (m, 2H, $3\gamma_2$ and $3\beta_2$), 1.40 (d, 3H, 1γ), 1.60 to 1.90 (m, 3H, $3\gamma_1$, $2\beta_1$ $2\beta_2$), 2.00 to 2.20 (m, 5H, $3\beta_1$, $5\beta_1$, $5\delta_1$, $5\delta_2$ and 1NH), 2.65 (m, 2H, $4\beta_2$ and $5\epsilon_2$), 2.80 [s, 6H, $N(CH_3)_2$], 3.15 (t, 1H, $4\beta_1$), 3.20 (s, 3H, NCH_3), 3.40 (d, 1H, 1α), 3.60 (t, 2H, $3\delta_1$ and $3\delta_2$), 3.70 to 4.00 (dd, 2H, 1'$\underline{CH_2}$-NH), 4.60 (m, 4H, 3α, 4α, 5α and $5\epsilon_1$), 4.85 (q, 1H, 2α), 5.70 (d, 1H, 6α), 5.80 (m, 1H, 1β), 6.35 (d, 2H, 4ϵ), 6.45 (d, 2H, 4δ), 7.30 [m, 6H, aromatic (6)], 7.45 (dd, 2H, 1'H_3 and 1'H_5), 7.90 (d, 1H, 2NH, D_2O exchanged), 8.50 (d, 1H, 6NH, D_2O exchanged), 8.80 (dd, 2H, 1'H_2 and 1'H_6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.8 (2γ), 16.4 (1γ), 24.1 (2β), 25.0 (3γ), 27.6 (3β), 30.8 (NCH_3), 35.5 (4β), 36.4 (5β), 38.5 (5δ), 40.2 [$N(CH_3)_2$], 40.3 (5ϵ), 47.5 (3δ), 49.1 (1'CH_2-NH), 50.5 (1α), 54.0 (2α), 56.3 (4α), 56.4 (5α), 57.1 (3α), 61.9 (6α), 71.5 (1β), 112.5 (4ϵ), 121.6 (4γ), 124.0 (4δ), 127.8, 128.5, 129.7 [1'H_3, 1'H_5 and CH, aromatic (6)], 136.0 [Cq, aromatic (6)], 148.4 (1'Cq), 150.0 [Cq-$N(CH_3)_2$], 150.3 (1'H_2 and 1'H_6), 168.2 to 172.0 (CO, amides and ester), 204.0 (5γ); MS (DCI): m/z = 837 (MH^+).

1-des-(3-hydroxy-picolinoyl)-1-(3-pyridyl)-methyl-pristinamycin I_A 29

When the controlled potential was fixed at -1150 mV s.c.e., method A applied to **6** (340 mg, 0.4 mmol) allowed the isolation of aminomethylpyridine **29** as an amorphous solid (67 mg, 20% yield, decomposes above 150°C) and that of compound **22** (15% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 0.00 (dd, 1H, $5\beta_2$), 0.90 (t, 3H, 2γ), 1.25 (m, 2H, $3\beta_2$ and $3\gamma_2$), 1.45 (d, 3H, 1γ), 1.60 to 1.90 (m, 3H, $2\beta_1$, $2\beta_2$ and $3\gamma_1$), 2.00 to 2.20 (m, 4H, $3\beta_1$, $5\beta_1$, $5\delta_1$ and $5\delta_2$), 2.65 (m, 2H, $4\beta_2$ and $5\epsilon_2$), 2.80 [s, 6H, $N(CH_3)_2$], 3.15 (t, 1H, $4\beta_1$), 3.25 (s, 3H, NCH_3), 3.40 (d, 1H, 1α), 3.55 (t, 2H, $3\delta_1$and $3\delta_2$), 3.70 to 4.00 (dd, 2H, 1'$\underline{CH_2}$-NH), 4.60 (m, 3H, 3α, 5α and $5\epsilon_1$), 4.75 (dd, 1H, 4α), 4.85 (q, 1H, 2α), 5.75 (d, 1H, 6α), 5.85 (m, 1H, 1β), 6.40 (s, 4H, 4ϵ and 4δ), 7.30 [m, 5H, aromatic (6)], 7.50 (m, 1H, 1'H_5), 7.90 (d, 1H, 2NH, D_2O exchanged), 8.00 (dt, 1H, 1'H_4), 8.55 (d, 1H, 6NH, D_2O exchanged), 8.60 (d, 1H, 1'H_2), 8.75 (dd, 1H, 1'H_6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7 (2γ), 17.5 (1γ), 25.0 (2β), 25.8 (3γ), 28.5 (3β), 31.7 (NCH_3), 36.3 (4β), 37.4 (5β), 39.5 (5δ), 41.1 [$N(CH_3)_2$], 41.2 (5ϵ), 48.2 (3δ), 48.4 (1'CH_2-NH), 51.4 (1α), 54.8 (2α), 57.1 (4α), 57.4 (5α), 58.0 (3α), 62.9 (6α), 72.3 (1β), 113.4 (4ϵ), 122.6 (4γ), 124.7 (1'H_5), 128.6, 129.3, 130.4 [CH, aromatic (6)], 136.0 [Cq, aromatic (6)], 137.0 (1'Cq), 137.7 (1'H_4), 150.1 (1'H_2), 150.7 (1'H_6), 151.0 [Cq-$N(CH_3)_2$], 169.0 to 172 (CO, amides and

ester), 203.0 (5γ); MS (DCI): m/z = 837 (MH^+).

1-des-(3-hydroxy-picolinoyl)-1-[1-(1,2,3,4-tetrahydroisoquinolyl)]-carbonyl-pristinamycin I_A 31

When E = -1000 mV s.c.e., method A applied to **9** (360 mg, 0.4 mmol) afforded compound **22** (15% yield) and tetrahydroisoquinoline **31** (163 mg, 45% yield, mp, 175 ± 2°C) as a mixture of two isomers A and B that could be separated.

Isomer A (25% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.55 (dd, 1H, $5\beta_2$), 0.95 (t, 3H, 2γ), 1.15 (d, 3H, 1γ), 1.20 to 1.40 (m, 2H, $3\beta_2$ and $3\gamma_2$), 1.60 to 1.80 (m, 3H, $2\beta_1$, $2\beta_2$ and $3\gamma_1$), 2.10 (m, 1H, $3\beta_1$), 2.20 to 2.40 (m, 3H, $5\beta_1$, $5\delta_1$ and $5\delta_2$), 2.80 [m, 3H, $5\epsilon_2$, 1'CH_2(4)], 2.85 [s, 6H, $N(CH_3)_2$], 2.95 (dd, 1H, $4\beta_2$), 3.05 [m, 2H, 1'CH_2(3)], 3.30 to 3.40 (m, 4H, NCH_3 and $4\beta_1$), 3.40 to 3.60 (m, 2H, $3\delta_1$ and $3\delta_2$), 4.60 (m, 2H, 3α and 1α), 4.80 [m, 3H, 2α, $5\epsilon_1$, 1'CH(1)], 5.15 (d, 1H, 5α), 5.35 (dd, 1H, 4α), 5.80 (m, 1H, 1β), 5.90 (d, 1H, 6α), 6.50 (d, 2H, 4ϵ), 6.70 (d, 1H, 2NH, D_2O exchanged), 7.05 (d, 2H, 4δ), 7.10 to 7.70 [m, 9H, aromatic (6), H(5), H(6), H(7) and H(8)], 8.10 (d, 1H, 1NH, D_2O exchanged), 8.70 (d, 1H, 6NH, D_2O exchanged); MS (DCI): m/z = 905 (MH^+).

Isomer B (20% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.40 (dd, 1H, $5\beta_2$), 0.90 (t, 3H, 2γ), 1.15 (m, 1H, $3\beta_2$), 1.35 (m, 4H, 1γ and $3\gamma_2$), 1.45 to 1.70 (m, 3H, $2\beta_1$, $2\beta_2$ and $3\gamma_1$), 2.10 (m, 1H, $3\beta_1$), 2.20 to 2.40 (m, 3H, $5\beta_1$, $5\delta_1$ and $5\delta_2$), 2.75 to 2.90 [m, 7H, $N(CH_3)_2$ and $5\epsilon_2$), 2.95 to 3.10 [m, 3H, 1'CH_2(4) and $4\beta_2$), 3.30 [m, 5H, 1'CH_2(3) and NCH_3], 3.40 to 3.70 (m, 3H, $3\delta_1$, $3\delta_2$ and $4\beta_1$), 4.60 (t, 1H, 3α), 4.70 [s, 1H, 1'CH(1)], 4.80 (m, 3H, $5\epsilon_1$, 2α and 1α), 5.20 (d, 1H, 5α), 5.30 (dd, 1H, 4α), 5.85 (m, 2H, 6α and 1β), 6.30 (d, 1H, 2NH, D_2O exchanged), 6.50 (d, 2H, 4ϵ), 7.05 (d, 2H, 4δ), 7.20 to 7.60 [m, 9H, aromatic (6), H(5), H(6), H(7) and H(8)], 8.00 (d, 1H, 1NH, D_2O exchanged), 8.50 (d, 1H, 6NH, D_2O exchanged). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0 (2γ), 17.5 (1γ), 25.0 (2β and 3γ), 29.0 (3β), 30.0 [1'CH_2(4)], 32.0 (NCH_3), 37.0 (4β), 38.0 (5ϵ), 40.0 (5δ), 41.0 [$N(CH_3)_2$], 41.5 (5β), 42.0 [1'CH_2(3)], 49.0 (3δ), 52.0 (2α), 55.0 (4α), 56.5 (1α), 57.0 (6α), 58.0 (5α), 58.5 (3α), 60.0 [1'CH_2(1)], 72.0 (1β), 113.5 (4ϵ), 123.0 (4γ), 127 to 130 [CH, aromatic (6), CH(5), CH(6), CH(7) and CH(8)], 131.0 (4δ), 132.0 and 135.0 (Cq, tetrahydroisoquinoline), 137.0 [Cq, aromatic (6)], 151.0 [Cq-$N(CH_3)_2$], 169.0 to 174.0 (CO amides and ester), 204.0 (5γ) ; MS (DCI): m/z = 905 (MH^+).

1-des-(3-hydroxypicolinoyl)-1-(1-methyl-3-oxo-pipecolinoyl)-pristinamycin I_A 32

When E = -1000 mV s.c.e., method A applied to **10** (352 mg, 0.4 mmol) afforded tetrahydropyridine **32** (212 mg, 60% yield, mp, 203 ± 2°C) as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.50 (dd, 1H, $5\beta_2$), 0.95 (t, 3H, 2γ), 1.20 to 1.40 (m, 5H, $3\beta_2$, $3\gamma_2$ and 1γ), 1.60 to 1.80 ($2\beta_1$, $2\beta_2$ and $3\gamma_1$), 1.95 [m, 2H, 1'CH_2(5)], 2.10 (m, 1H, $3\beta_1$), 2.20 to 2.35 (m, 3H, $5\beta_1$, $5\delta_1$ and $5\delta_2$), 2.45 [t, 2H, 1'CH_2(4)], 2.60 [s, 3H, NCH_3 (tetrahydropyridine ring)], 2.70 to 3.00 [m, 10H, 1'CH_2(6), $4\beta_2$, $5\epsilon_2$ and $N(CH_3)_2$], 3.20 to 3.40 (m, 5H, $3\delta_2$, $4\beta_1$ and NCH_3), 3.55 (m, 1H, $3\delta_1$), 4.55 (t, 1H, 3α), 4.75 (m, 1H, $5\epsilon_1$), 4.85 (m, 2H, 1α and 2α), 5.10 (broad s, 1H, 5α), 5.20 (broad d, 1H, 4α), 5.90 (m, 2H, 1β and 6α), 6.50 (d, 1H, 2NH, D_2O exchanged), 6.60 (d, 2H, 4ϵ), 7.10 (d, 2H, 4δ), 7.10 (d, 1H, 1NH, D_2O exchanged), 7.20 to 7.40 [m, 5H, aromatic (6)], 8.70 (d, 1H, 6NH, D_2O exchanged), 12.10 (s, 1H, OH, D_2O exchanged). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5 (2γ), 17.0 [1'CH_2(5)], 18.0 (1γ), 25.0 (2β), 26.0 (3γ), 27.0 [1'CH_2(4)], 28.0 (3β), 32.0 (NCH_3), 36.5 (4β), 38.0 (5β), 40.0 (5δ), 41.0 [$N(CH_3)_2$], 42.0 (5ϵ), 44.0 [NCH_3, tetrahydropyridine ring], 48.0 (3δ), 51.8 [1'CH_2(6)], 52.0 (5α), 55.0 (2α), 56.5 (1α), 57.0 (3α), 57.5 (6α), 58.0 (4α), 72.5 (1β), 113.0 (4ϵ), 116.0 [1'Cq(2)], 123.0 (4γ), 128.0 (4δ), 128.5, 129.0 and 131.0 [CH, aromatic (6)], 137 [Cq, aromatic (6)], 151.0 [Cq-$N(CH_3)_2$], 164.0 [1'Cq(3)], 168.0 to 173.0 (CO amides and ester), 204 (5γ); MS (DCI): m/z = 885 (MH^+).

1-des-(3-hydroxypicolinoyl)-1-(1-oxo-2-cyclopentene-2-yl)-carbonyl-pristinamycin I_A 33

Method A applied to **10** (352 mg, 0.4 mmol) afforded compound **33** (35 mg, 10% yield, mp, 182 ± 2°C) as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65 (dd, 1H, $5\beta_2$), 0.90 (t, 3H, 2γ), 1.10 to 1.30 (m, 5H, $3\beta_2$, $3\gamma_2$ and 1γ), 1.50 to 1.80 (m, 3H, $3\gamma_1$, $2\beta_1$ and $2\beta_2$), 2.00 (m, 1H, $3\beta_1$), 2.10 to 2.40 (m, 3H, $5\delta_1$, $5\delta_2$ and $5\beta_1$), 2.60 [m, 2H, 1'CH_2(5)], 2.80 [m, 3H, $5\epsilon_2$, 1'CH_2(4)], 2.85 [s, 6H, N(CH_3)$_2$], 2.95 (dd, 1H, $4\beta_2$), 3.20 to 3.40 (m, 5H, $3\delta_2$, $4\beta_1$ and NCH_3), 3.50 (m, 1H, $3\delta_1$), 4.60 (m, 1H, 3α), 4.70 (m, 1H, $5\epsilon_1$), 4.80 (q, 1H, 2α), 5.0 (dd, 1H, 1α), 5.45 (dd, 1H, 4α), 5.75 (d, 1H, 5α), 5.90 (m, 2H, 6α and 1β), 6.45 (d, 1H, 2NH, D_2O exchanged), 6.60 (d, 2H, 4ε), 7.10 (d, 2H, 4δ), 7.15 to 7.40 [m, 5H, aromatic (6)], 8.60 (d, 1H, 1NH, D_2O exchanged), 8.70 [t, 1H, 1'H(3)], 8.85 (d, 1H, 6NH, D_2O exchanged). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5 (2γ), 17.0 (1γ), 25.0 (3γ), 25.5 (2β), 27.0 [1'CH_2(4)], 28.0 (3β), 31.5 (NCH_3), 36.0 (4β), 36.5 [1'CH_2(5)], 37.5 (5ϵ), 39.5 (5δ), 41.0 [N(CH_3)$_2$], 42.0 (5β), 48.0 (3δ), 52.0 (2α), 54.0 (4α), 56.0 (1α), 56.5 (6α), 57.5 (5α), 72.0 (1β), 113.0 (4ϵ), 123.5 (4γ), 128.0, 128.5 and 129.0 [CH, aromatic(6)], 131.0 (4δ), 137.0 [1'Cq(2)], 137.5 [Cq, aromatic(6)], 151.0, [Cq-N(CH_3)$_2$], 162.0 to 173.0 (CO amides and ester), 175.0 [1'CH(3)], 205.0 (5γ), 208.0 [1'CO(1)]; MS (DCI): m/z = 854 (MH^+).

N-phenyl-1-methyl-3-oxo-pipecolinamide 34

200 mL of an hydroalcoholic (50:50) sulphuric acid solution (0.5 mol.L^{-1}) of compound **11** (91 mg, 0.4 mmol) was reduced, under nitrogen, at 25°C, at a mercury pool working electrode (E = -1000 mV s.c.e.). After exhaustive electrolysis, the hydroalcoholic solution was concentrated to 100 mL under reduced pressure at 40°C. The resulting solution was neutralized by a sodium carbonate solution (5 mol.L^{-1}) and extracted with dichloromethane (200 mL). The organic phase was dried over anhydrous sodium sulphate and the solvent removed under reduced pressure at 30°C.

Chromatography [dichloromethane:methanol (99:1)] afforded tetrahydropyridine **34** (56 mg, 60%) as a yellow-coloured oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.90 (m, 2H, CH_2(5)], 2.30 [t, 2H, CH_2(4), J = 7 Hz], 2.50 (s, 3H, CH_3), 2.90 [t, 2H, CH_2(6), J = 6 Hz], 7.10 [t, 1H, H(4'), J = 8 Hz], 7.35 [t, 2H, H(3') and H(5'), J = 8 Hz], 7.60 [d, 2H, H(2') and H(6'), J = 8 Hz], 8.70 (s, 1H, NH, D_2O exchanged), 12.2 (s, 1H, OH, D_2O exchanged); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1 [CH_2(5)], 26.2 [CH_2(4)], 42.8 (CH_3), 50.6 [CH_2(6)], 116.0 (C-2), 119.8 [CH(2') and CH(6')], 124.1 [CH(4')], 128.9 [CH(3') and CH(5')], 137.4 (C-1'), 163.0 (C-3), 167.8 (CO, amide); MS (DCI): m/z = 233 (MH^+).

N-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 36

The same procedure applied to **12** (100 mg, 0.4 mmol) afforded, after chromatography [diethyl oxide:cyclohexane (50:50)], compound **36** (27 mg, 27% yield, mp, 147 ± 2°C) as an amorphous solid along with aniline **35** (45% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (broad s, 1H, NH, D_2O exchanged), 2.70 to 2.90 [m, 2H, CH_2(4)], 3.15 [m, 2H, CH_2(3)], 4.70 [s, 1H, H(1)], 7.00 to 7.20 [m, 4H, H(4'), H(5), H(6), and H(7)], 7.30 [t, 2H, H(3') and H(5'), J = 8 Hz], 7.55 [d, 2H, H(2') and H(6'), J = 8 Hz], 7.70 [dd, 1H, H(8), J = 6 Hz], 9.40 [s, 1H, NH(amide) D_2O exchanged]. ^{13}C NMR (75 MHz, $CDCl_3$); δ 29.2 [CH_2(4)], 41.1 [CH_2(3)], 60.2 [CH(1)], 119.3 [CH(2') and CH(6')], 124.0 [CH(4')], 126.0, 127.0, 128.1 and 129.0 [CH(5), CH(6), CH(7) and CH(8)], 128.8 [CH(3') and CH(5')], 131.8 and 134.5 (Cq, tetrahydroisoquinoline), 137.8 (C-1'), 170.7 (CO, amide); MS (DCI): m/z = 253 (MH^+).

N-(4-cyano-phenyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 38

The same procedure applied to **13** (109 mg, 0.4 mmol) afforded after chromatography [diethyl oxide:cyclohexane (60:40)] compound **38** (22 mg, 20% yield, mp, 140 ± 2°C) as an amorphous solid along with 4-cyanoaniline **37** (40% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (broad s, 1H, NH, D_2O exchanged), 2.80 to 2.95 [m, 2H, CH_2(4)], 3.20 [t, 2H, CH_2(3), J = 6 Hz], 4.70 [s, 1H, H(1)], 7.10 to 7.30 [m, 3H, H(5), H(6) and H(7)], 7.60 [m, 3H, H(8), H(3') and H(5')], 7.70 [d, 2H, H(2') and H(6')], 9.80 [broad s, 1H, NH (amide), D_2O exchanged]. ^{13}C NMR (75 MHz, $CDCl_3$); δ 29.2 [CH_2(4)], 41.1 [CH_2(3)], 60.0 [CH(1)], 106.8 (C-4'), 118.9 (CN), 119.3 [CH(2') and CH(6')], 126.1, 127.3, 128.2 and 129.1 [CH(5), CH(6), CH(7) and CH(8)], 131.0 and 134.5 (Cq, tetrahydroisoquinoline), 133.1 [CH(3') and CH(5')], 141.8 (C-1'), 171.4 (CO, amide); MS (DCI): m/z = 278 (MH^+).

N-(4-methoxy-phenyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 40

The same procedure applied to **14** (111 mg, 0.4 mmol) afforded after chromatography [diethyl oxide:cyclohexane (60:40)] compound **40** (38 mg, 33% yield, mp, 172 ± 2°C) as an amorphous solid along with 4-methoxyaniline **39** (50% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (broad s, 1H, NH, D_2O exchanged), 2.80 to 3.00 [m, 2H, CH_2(4)], 3.15 [m, 2H, CH_2(3)], 3.90 (s, 3H, OCH_3), 4.70 [s, 1H, H(1)], 6.85 [d, 2H, H(3') and H(5'), J = 9 Hz], 7.10 to 7.25 [m, 3H, H(5), H(6) and H(7)], 7.50 [d, 2H, H(2') and H(6'), J = 9 Hz], 7.65 [m, 1H, H(8)], 9.30 [broad s, 1H, NH (amide), D_2O exchanged]. ^{13}C NMR (75 MHz, $CDCl_3$); δ 29.3 [CH_2(4)], 41.2 [CH_2(3)], 55.4 (OCH_3), 60.2 [CH(1)], 114.0 [CH(3') and CH(5')], 121.0, [CH(2') and CH(6')], 126.0, 127.0, 128.1 and 129.0 [CH(5), CH(6), CH(7) and CH(8)], 131.0 and 134.5 (Cq, tetrahydroisoquinoline), 132.0 (C-1'), 156.1 (C-4'), 170.5 (CO, amide); MS (DCI): m/z = 283 (MH^+).

N-(2,6-dimethyl-phenyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 42

The same procedure applied to **15** (110 mg, 0.4 mmol) afforded after chromatography [diethyl oxide:cyclohexane (40:60)] compound **42** (56 mg, 50% yield, mp, 131 ± 2°C) as an amorphous solid along with 2,6-dimethylaniline **41** (10% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 6H, CH_3), 2.90 (broad s, 1H, NH, D_2O exchanged), 3.30 to 3.90 [m, 4H, CH_2(4) and CH_2(3)], 5.30 [s, 1H, H(1)], 7.50 [m, 3H, H(3'), H(5') and H(4')], 7.60 to 7.80 [m, 3H, H(5), H(6) and H(7)], 8.20 [m, 1H, H(8)], 9.20 [s, 1H, NH (amide), D_2O exchanged]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.3 (CH_3), 29.4 [CH_2(4)], 41.4 [CH_2(3)], 60.6 [CH(1)], 125.9, 126.8, 126.9, 127.7 and 129.0 [CH(4'), CH(5), CH(6), CH(7) and CH(8)], 128.0 [CH(3') and CH(5')], 132.2 and 134.5 (Cq, tetrahydroisoquinoline), 133.7 (C-1'), 134.9 (C-2' and C-6'), 171.2 (CO, amide); MS (DCI): m/z = 281 (MH^+).

N-(2,6-diisopropyl-phenyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 43

The same procedure applied to **16** (139 mg, 0.4 mmol) afforded after chromatography [diethyl oxide:cyclohexane (30:70)] compound **43** (106 mg, 75% yield, mp, 143 ± 2°C) as an amorphous solid. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.05 [d, 12H, CH_3 (isopropyl)], 2.35 (broad s, 1H, NH, D_2O exchanged), 2.80 to 3.25 [m, 6H, CH (isopropyl), CH_2(4) and CH_2(3)], 4.80 [s, 1H, H(1)], 7.15 [m, 6H, H(3'), H(4'), H(5'), H(5), H(6) and H(7)], 7.65 [dd, 1H, H(8), J = 6 Hz, J = 2 Hz], 8.55 [s, 1H, NH(amide), D_2O exchanged]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.3 (CH_3, isopropyl), 28.4 (CH, isopropyl), 29.5 [CH_2(4)], 41.5 [CH_2(3)], 60.8 [CH(1)], 123.0 [CH(3') and CH(5')], 125.8, 126.8, 127.5, 127.8, 128.9 [CH(4'), CH(5), CH(6), CH(7) and CH(8)],

131.1 (C-1'), 132.0 and 134.5 (Cq, tetrahydroisoquinoline), 145.7 (C-2' and C-6'), 172.4 (CO, amide); MS (DCI): m/z = 353 (MH^+).

N-(2,6-diisopropyl-phenyl)-3-methoxy-1,2,5,6-tetrahydropicolinamide 45

The same procedure applied to **19** (125 mg, 0.4 mmol) afforded after chromatography [toluene:acetone (95:5)], compound **45** (38 mg, 30% yield, mp, 159 ± 2°C) as an amorphous solid along with 2,6-diisopropylaniline **44** (50% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 [d, 12H, CH_3 (isopropyl), J = 6 Hz], 2.15 [m, 2H, CH_2(5)], 2.60 (broad s, 1H, NH, D_2O exchanged), 2.80 [m, 2H, CH_2(6)], 2.90 [septuplet, 2H, CH (isopropyl), J = 6 Hz], 3.60 (s, 3H, OCH_3), 3.95 [s,1H, H(2)], 4.90 [t, 1H, H(4), J = 4 Hz], 7.10 [d, 2H, H(3') and H(5'), J = 8 Hz], 7.20 [t, 1H, H(4'), J = 8 Hz], 7.85 (s, 1H, NH (amide), D_2O exchanged]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.5 (CH_3, isopropyl), 23.7 [CH_2(5)], 28.6 (CH, isopropyl), 40.7 [CH_2(6)], 54.3 (OCH_3), 58.7 [CH(2)], 95.3 [CH(4)], 123.3 [CH(3') and CH(5')], 128.0 [CH(4')], 131.2 (C-1'), 145.9 (C-2' and C-6'), 151.0 (C-3), 170.3 (CO, amide); MS (DCI): m/z = 317 (MH^+).

Benzylaniline 46

When the potential was fixed at -1150 mV s.c.e., the same procedure applied to **20** (79 mg, 0.4 mmol) afforded after chromatography [dichloromethane:cyclohexane (60:40)] benzylaniline **46** (15 mg, 20% yield), as well as a noticeable amount of non reacted benzanilide **20** (45% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 4.00 (broad s, 1H, NH, D_2O exchanged), 4.30 (s, 2H, CH_2), 6.60 [d, 2H, H(2') and H(6'), J = 8 Hz], 6.70 [t, 1H, H(4'), J = 8 Hz], 7.15 [t, 2H, H(3') and H(5'), J = 8 Hz], 7.35 [m, 5H, CH (aromatic, benzyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 48.3 (CH_2), 112.8 [CH(2') and CH(6')], 117.5 [CH(4')], 127.2 [CH(4)], 127.5, 128.6 and 129.2 [CH(3'), CH(5') and CH (aromatic, benzyl), 139.4 (C-1), 148.1 (C-1'); MS (DCI): m/z = 184 (MH^+).

N-benzyl-4-cyano-aniline 47

When the potential was fixed at -1150 mV s.c.e., the same procedure applied to **21** (89 mg, 0.4 mmol) afforded after chromatography [dichloromethane:cyclohexane (60:40)] compound **47** (50 mg, 60% yield, mp, 64 ± 2°C) as an amorphous solid along with non reacted N-(4-cyano-phenyl)-benzamide **21** (20% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 4.35 (d, 2H, CH_2, J = 6 Hz), 4.70 (t, 1H, NH, J = 6 Hz, D_2O exchanged), 6.60 [d, 2H, H(2') and H(6'), J = 8 Hz], 7.35 [m, 7H, H(3'), H(5') and CH (aromatic, benzyl)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 47.3 (CH_2), 99.0 (C-4'), 112.3 [CH(2') and CH(6')], 120.3 (CN), 127.2, 127.5 and 128.7 [CH (aromatic, benzyl)], 133.6 [CH(3') and CH(5')], 137.7 (C-1), 151.1 (C-1'); MS (DCI): m/z = 209 (MH^+).

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