Derivatives of pyrido[3´,2´:4,5]pyrrolo[1,2-*c*]pyrimidones

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Dedicated to Professor Enrique Melendez

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Abstract

Different *N*-protected dichloromethanimines have been used for the preparation of pyrido[3´,2´:4,5]pyrrolo[1,2-*c*]pyrimidines and the results are compared. The preparation of 4-chloro-9-tosylaminopyrido[3´,2´:4,5]pyrrolo[1,2-*c*]pyrimidine is described.

Keywords: Variolins, pyrido[3´,2´:4,5]pyrrolo[1,2-*c*]pyrimidines, *N*-protected-dichloroimines, heterocycles

Introduction

The synthesis of variolin B [1] **1** and derivatives has been one of the important topics developed in our laboratory during the last years.[2] Our previous synthetic procedure described for the preparation of deoxyvariolin B **2** is based on the construction of the tricyclic system of pyrido[3´,2´:4,5]pyrrolo[1,2-*c*]pyrimidone, followed by the transformation of the pyrimidone C ring into an *N*-protected-aminopyrimidine, halogenation at position 5 of the tricyclic system and finally a palladium cross-coupling reaction for the introduction of the fourth heteroaromatic D ring (Scheme 1).

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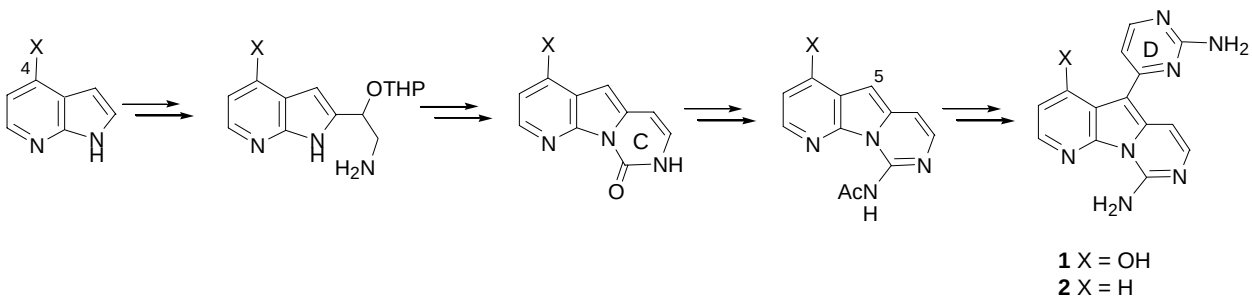


Scheme 1. Synthesis of deoxyvariolin B[2a].

The application of that procedure to the total synthesis of variolin B **1** required as starting material a properly 4-substituted-7-azaindole. Two different substituents at position four of 7-azaindole were used for this purpose, a methoxy group and a chlorine. Both functional groups could be transformed into the hydroxy group, characteristic of the natural product, in a late synthetic step. The hydroxy-functionality could be unmasked by either *O*-demethylation of the methoxy derivative or by a nucleophilic substitution on the π-deficient pyridine ring.[3] In this paper we describe our results on the preparation and use of 4-chloropyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine system for the above-mentioned synthesis.

The efficient synthetic procedure described for the preparation of deoxyvariolin B[2a] based in the use of triphosgene to afford the tricyclic system had, for its application to the synthesis of variolin B derivatives, the inconvenience of the strong conditions needed for the transformation of the pyrimidone into the aminopyrimidine. In these conditions, either the methoxy or chlorine groups were partially or totally displaced. This made it imperative to modify the conditions of ring C formation using a synthetic equivalent of triphosgene in which a protected nitrogen was introduced at the same time that ring C was formed. In this paper we describe the use of dichloromethanimine with different *N*-protecting/blocking groups **3a-e** for the construction of the properly fuctionalized and protected aminopyrimidine ring C of variolin B and derivatives.

Results and Discussion

The use of *N*-protected dichloromethanimines **3**, as synthetic equivalents of triphosgene, has the advantage of using the same synthetic strategy as described before, but of decreasing the number of steps and, most importantly eliminating the need for the transformation of pyrimidones into the aminopyrimidines and the high pressuree conditions needed for that. The choice of the nitrogen protecting group was crucial for the process because it was required to be stable not only during the formation of the ring C but also in the deprotection of the *O*-tetrahydropyranyl group, the dehydration of the resulting alcohol, during the halogenation at position 5 of the

tricyclic system, and in the cross-coupling reaction employed for the introduction of the fourth aromatic ring.

As possible *N*-protecting/blocking groups we examined acyl, alkyl and sulfonyl substituents. Thus we prepared dichloromethanimines in which the *N*-substituent was dichloroacetyl **3a**, acetyl **3b,** triphenylmethyl (trityl, Tr) **3c**, *p*-methoxyphenylmethyl **3e**, and *p*-toluenesulfonyl (tosyl, Ts) **3d**.

The procedure for the preparation of these dichloromethanimines was different depending on the *N*-substituent and the starting material, and three different alternatives were employed. The methods used are summarized in Table 1.

Table 1. Structure and preparation of *N*-substituted dichloromethanimines 3a-e

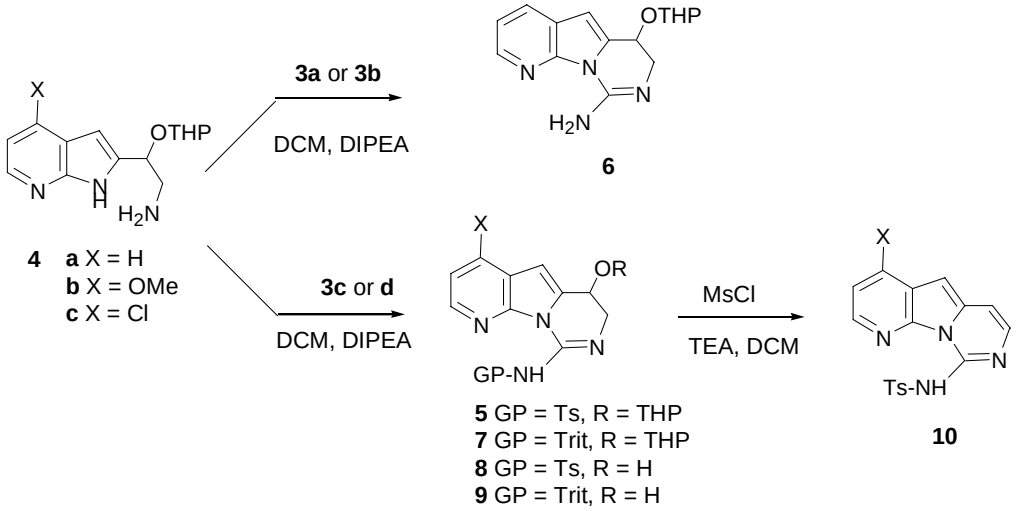
PG-N=CCl_2	Protecting Group	Starting Material	Method[a]	Ref.
3a	Cl_2CHCO-	Cl_2CHCO-NCS[4]	A	4
3b	CH_3CO-	CH_3CO-NCS[4]	A	4
3c	Tr-	Tr-NHCHO[5]	B	---
3d	Ts-	Ts-N=$C(SMe)_2$[6]	C	6
3e	*p*-$MeOC_6H_4CH_2$-	*p*-$MeOC_6H_4CH_2$-NHCHO[4]	B	---

[a] A: reaction with Cl_2 catalyzed with $TiCl_4$; B: reaction with $SOCl_2$ and SO_2Cl_2 until ^{1}H NMR analysis indicated the absence of signals for CHO; C: reaction with Cl_2 in CCl_4 as solvent at 0 ºC until ^{1}H NMR analysis indicated the absence of signals for SMe.

Addition of chlorine to acetyl isothiocyanate using $TiCl_4$ as catalyst to give *N*-acetyldichloromethanimine **3b** was also used for the preparation of *N*-dichloroacetyldichloromethanimine. The *N*-tosyldichloromethanimine **3d**[6] was obtained from toluene-4-sulfonamide by transformation into *N*-tosyl-bis(methylsulfanyl)methanimine and then treatment of this derivative with chlorine, following the procedure described by Heukelbach. The *N*-alkyldichloromethanimines substituted with trityl **3c** and *p*-methoxybenzyl **3e** as protecting groups were prepared from the appropriate *N*-alkylformamides by reaction with a mixture of thionyl chloride and sulfuryl chloride. These reaction conditions also afforded **3c**, not previously described, in a good yield and purity. The formation of **3c** was verified by comparison of its ^{1}H- and ^{13}C-NMR spectra with the comparable signals of the precursor *N*-tritylformamide,[7] This amide has a characteristic doublet at 8.05 ppm with a coupling constant of 12 Hz due to the formyl proton that disappears in the dichloro-compound; the corresponding carbon signal shifted from 165.9 ppm for the NHCO precursor to 81.3 ppm in TrN=CCl_2. Dichloro-imine **3c** was used without purification in the cyclisation reactions. When the same reaction conditions were used

with *p*-methoxybenzylformamide a mixture of the desired dichloro-imine **3e** and a trichloro-derivative with an extra chlorine, presumably at the benzylic position, was obtained and the possible use of this dichloroimine was not examined further.

Reaction of aminoethylazaindole **4a**[2c] with **3a-d** for the transformation into the tricyclic system was carried out using comparable reaction conditions for all the dichloromethaninimes (Scheme 2), in DCM as a solvent at room temperature using *N,N*-diisopropylethylamine (DIPEA).



Scheme 2. Preparation of substituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidines.

When the *N*-acetyl or *N*-dichloroacetyldichloromethanimines were used for the cyclisation, *N*-deacylation took place during the isolation procedure and only small amounts of the 9-amino-6,7-dihydropyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine **6** could be isolated.[8] Additionally, compound **6** was not easy to handle, probably because of its high polarity. The low yields obtained with these protected dichloromethanimines and what would have been a need for a new protection, following the cyclisation, to allow the synthesis to proceed further, persuaded us to change to the use of an alternative dichloromethanimine.

The *N*-tosyl- and *N*-trityldichloromethanimines gave better results. With both these dichloromethanimines, tricyclic systems, **5a** and **7a**, were obtained in 71% and 58% yields, respectively. From the synthetic point of view it was not a problem to have **5a** and **7a** as a diastereomeric mixture, as well as compound **4**, because the two diasterogenic centres disappear later in the synthetic sequence. The differing polarities of the two **7a** diastereomers was enough to allowed the isolation of each isomer during the purification and thence the spectroscopic characterization of each isomer, singly. It is tempting to assign the relative configurations of the stereocenters on the basis of a comparison of the distances (d) in Å[9] between H6 and H2' of both isomers and the percentage increase in the areas of the signals in an NOE-DIF experiment, taking

into consideration that the nuclear Overhauser effect (NOE) is a function of the distance between the atoms which give a positive NOE. As show figure 1 the distance between H6 and H2' (d = 3.604 Å) in the **(6RS, 2'SR)-7a** is larger than in **(6SR, 2'SR)-7a** (d = 2.078 Å) and correspondingly, the increase in area of H2' on irradiation H6 is smaller (6.61%) than the increase in in the area of H2' on irradiation of H6 in the other stereoisomer, **(6SR, 2'SR)-7a** (9.45%).

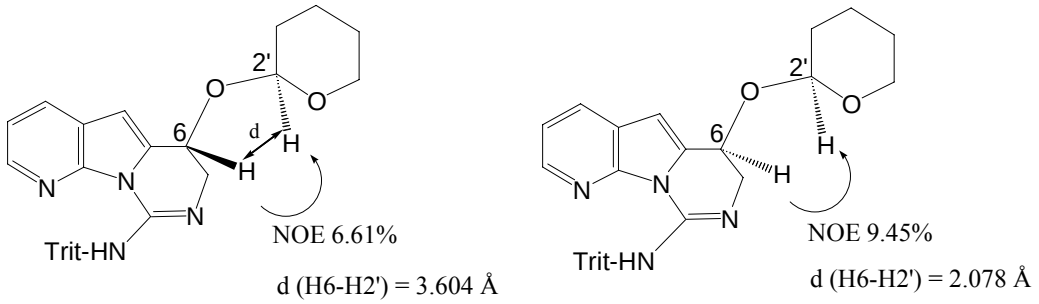


Figure 1

The following step required removal of the tetrahydropyranyl-protecting group and was done using 4N aq. HCl in DCM at reflux to give the alcohols **8a**[2c] and **9a** in good yields. At this point we also tested the formation of ring C from **4b** using **3c** and **3d** to give the protected alcohols **5b** and **7b** which were also deprotected, using the same conditions, to give the alcohols **8b** and **9b**. With the elimination of the *O*-protecting group, the resulting alcohols **8a-b** and **9a-b** gave easily assignable ^{1}H NMR spectra, with the disappearance of the second chiral centre. The MS of dihydro-derivatives **7a,b** and **9a,b** did not show molecular ions because of a very favoured fragmentation to generate ions at M+1-TritN as well as at 243 (trityl$^+$) as the base peak.

Whereas the dehydration of **8a** and **8b** was achieved by treatment with mesyl chloride and triethylamine (TEA) as base in DCM at room temperature giving the totally aromatic systems **10a** or **10b** with good yields, the *N*-trityl protected alcohols **9a** and **9b** under the same conditions were not significantly changed, even after a longer time and at a higher temperature. The corresponding aromatic compounds were produced, but in low yields and their isolation was difficult, and we were only able to characterize them by ^{1}H-NMR[10] and MS measurements. The difference in the methansulphonic acid elimination reaction was attributed to the withdrawing character of the tosyl protecting group compared with the donor effect of the trityl.

Much better synthetic results and workability were obtained using the Ts-N=CCl_2 **3d** and it became the reagent of choice for this key cyclisation process being employed in our total synthesis of the natural compound **1**[2c] and also for the preparation chloro-compound **9c**.

The chloro-compound **9c** was of interest to us as a potential precursor of a series of derivatives with different substituents in position 4 of the tricyclic system, to be obtained by nucleophilic displacement of the halogen.

The chloroamine **4c** was obtained from the 4-chloro-7-azaindole[11] by reaction of its 2-lithio derivative with 2-phthalimidoacetaldehyde.[12] A lithium-carboxylate was used as *N*-protecting

and *ortho*-directing substituent for the lithiation at position 2. The yield in this condensation was considerably inferior to those using 7-azaindole or 4-methoxy-7-azaindole. It was possible to recover part of the starting material, but there was a significant overall loss of material probably resulting from a competitive process involving the chlorine. Protection of the alcohol generated, by reaction with dihydropyran, and deprotection of the amino group by hydrazinolysis gave the amino-acetal **4c** as a mixture of diastereomers. Cyclization of **4c** with Ts-N=CCl_2 under the same conditions as before gave the 9-tosylaminopyrimidine **5c** in 68% yield. Removal of the *O*-tetrahydropyranyl protecting group by treatment with 4N HCl followed by elimination of the hydroxyl group through its mesylate gave **10c**, with slightly inferior yields than in the comparable steps starting with 7-azaindole or 4-methoxy-7-azaindole.

Conclusions

Several dichloromethanimines **3a-d** which differ in the *N*-protecting/blocking group have been tested for the preparation of amino-protected 9-aminopyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidines. This method for the synthesis of the tricyclic common core of the variolins has reduced the number of steps, and the tosyl protecting group was more efficient because it gave better reaction yields and remained untouched throughout the subsequent synthetic steps.

The chloro-compound **9** was prepared starting from the 4-chloro-7-azaindole following the same strategy as before. The overall synthetic yield was lower than the yields obtained in the preparation of analogous compounds without chlorine or with a methoxy in the 4–position, however we now have a procedure which will allow us to synthesise analogues of variolin B, utilising the reactivity of the halogen at the γ-position of the pyridine unit.

Experimental Section

General Procedures. Melting points were determined in open capillaries with a Gallenkamp Melting Point apparatus and are uncorrected. TLC was carried out on SiO_2 (silica Gel 60 F_{254}, Merck 0.063-0.200 mm) and spots were located with UV light. Column chromatography was carried out on SiO_2 (silica Gel 60 SDS 0.060-0.2 mm). Flash chromatography was carried out on SiO_2 (silica Gel 60 A CC, Merck). Organic extracts were dried over anhydrous sodium or magnesium sulfate, and solutions were evaporated under reduced pressure with a rotatory evaporator. IR spectra were performed on a Nicolet 205 FT-IR spectrometer. NMR spectra were measured with Varian Gemini-200, Varian Gemini-300, Varian Mercury-400 and Varian VXR-500 spectrometers; data are given in ppm referenced to TMS. Mass spectra were measured on a Hewlett-Packard model 5989A for chemical ionisation (CI) with methane (CH_4, as reactive gas) and electron impact (EI), on a Hewlett-Packard model 5890A for chemical ionisation with ammonia (NH_3), on a Fisons Instruments VG-Quattro for electrospray (ES) (performed with

H_2O/CH_3CN+1%formic acid as solvent) and on a Micromass Platform machine for atmospheric pressure chemical ionisation (APCI). High resolution mass spectra were performed on a Autospec/VG by Departament de Química Orgánica Biològica (C.S.I.C.) Barcelona and on a Micromass Autoespec by Unidade de Espectrometría de masas, Universidade de Santiago de Compostela. Elemental analyses were performed on a C. E. Instruments EA-1108 in the Serveis Científico-Tècnics de la Universitat de Barcelona.

4-Chloro-2-(1-hydroxy-2-phthalimidoethyl)-7-azaindole. To a cooled (-78 ^oC) solution of 4-chloro-7-azaindole (5 g, 33 mmol) in dry THF (100 mL) *n*-BuLi (20 mL, 1.6 M in hexane) was added and the mixture was stirred for 10 min. Dry CO_2 was bubbled through the mixture for 40 min. The solvent was evaporated and the residue was dissolved in dry THF (250 mL). The solution was cooled at -78 ^oC and *t*-BuLi (20 mL, 1.7 M in hexane) was added. The mixture was stirred for 20 min. A solution of *N*-(2,2-dimethoxyethyl)phthalimide (7.5 g, 39 mmol) in THF (140 mL) was added slowly. After 1.5 h. the reaction was quenched with saturated aq. NH_4Cl (80 mL) and the organic solvent evaporated. The mixture was dissolved in CH_2Cl_2 and washed with water. The organic solution was dried and evaporated. The mixture was purified by flash column chromatography. Elution with CH_2Cl_2/acetone (95/5) gave the starting 4-chloro-7-azaindole (3 g, 60%) and with CH_2Cl_2/MeOH (98/2) afforded the title compound (2.5 g, 21%) as a white solid. mp 190-191 ºC. IR (KBr) δ 3200 (NH/OH), 1759 (CO). ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 3.94 (dd, *J* 13.2 and 7.5, 1H, H2'), 3.95 (dd, *J* 13.2 and 6.5, 1H, H2'), 5.00 (ddd, *J* 7.5, 6.5, and 5.6, 1H, H1′), 5.92 (d, *J* 5.6, 1H, OH), 6.41 (s, 1H, H3), 7.14 (d, *J* 5.6, 1H, H5), 7.84 (m, 4H, Phth), 8.1 (d, *J* 5.6, 1H, H6), 11.65 (br, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75 MHz) δ 43.6 (t, C2′), 64.3 (d, C1′), 94.9 (d, C5), 115.3 (d, C3), 118.7 (s, C3a), 123.0 (d, Ph-β), 131.6 (s, Ph-ipso), 133.3 (s, C2), 134.3 (d, Ph-α), 142.2 (s, C7a*), 142.8 (d, C6), 149.1 (s, C4*), 167.7 (s, Ph-CO). MS (CI) *m/z* 344 (12), 343 (10), 342 (M+1, 36), 341 (13), 326 (41), 324 (100), 181 (30), 148 (43). *M+H* calculated for $C_{17}H_{13}ClN_3O_3$: 342.0645; HRMS found: $(M+H)^+$ 342.0642.

4-Chloro-2-[2-phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole. To a solution of 4-chloro-2-(1-hydroxy-2-phthalimidoethyl)-7-azaindole (10.2 g, 32.8 mmol) in $CHCl_3$ (1 L) and a 6N solution of HCl in dry benzene(180 mL) 2,3-dihydropyran (46mL, 330 mmol) was added. The mixture was refluxed for 3 h. After cooling the mixture was washed with saturated aq. $NaHCO_3$, dried and evaporated. The residue was purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (98.5/1.5) gave the title compound (10.8 g, 87%) as a diastereomeric mixture (1:1) as a white solid. IR (film) δ 1717 (CO). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02-1.80 (m, 6H, H3″, H4″ and H5″), 3.24-3.43 (m, 2H, H2′), 3.95, 4.03, 4.24 and 4.38 (dd, *J* 14.1 and 4.7, dd, *J* 14.1 and 5.6, dd, *J* 14.1 and 9.4 and dd, *J* 12.7 and 9.4, 2H, H6″), 4.72 and 4.92 (dd, *J* 3.1 and 2.8 and dd, *J* 3.4 and 3.0, 1H, H2″), 5.30 and 5.39 (dd, *J* 8.4 and 4.2 and dd, *J* 9.2 and 4.0, 1H, H1′), 6.56 and 6.62 (2 brs, 1H, H3), 7.13 and 7.20 (d, *J* 5.2 and d, *J* 5.2, 1H, H5), 7.71 (m, 2H, Ph-β), 7.85 (m, 2H, Ph-α), 8.35 and 8.55 (d, *J* 5.2 and d, *J* 5.2, 1H, H6). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 18.9 and 19.8 (t, C3″*), 25.0 and 25.3 (t, C4″*), 30.2 and 30.8 (t, C5″*), 41.8 and 42.8 (t, C6″), 61.8 and 63.5 (t, C2′), 69.2 and 71.6 (d, C1′), 95.5 and 96.4 (d,

C2”), 98.8 and 100.7 (d, C3), 116.1 (d, C5),120.6 and 120.7 (s, C3a), 123.1 and 123.3 (d, Ph-β), 131.7 and 131.9 (s, Ph-ipso), 133.9 and 134.0 (d, Ph-α), 136.1 and 137.4 (s, C2), 138.4 (s, C4**),143.3 and 143.4 (d, C6), 143.3 (s, 7a**), 167.8 (s, Ph-CO). MS (CI) *m/z* 428 (12), 427 (8), 426 (M+1, 29), 425 (4), 400 (21), 344 (12), 342 (38), 326 (20), 324 (52), 85 (100). *M+1* calculated for $C_{22}H_{21}ClN_3O_4$: 426.1221; HRMS found: M^+ 426.1226.

2-[2-Amino-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-4-chloro-7-azaindole (4c). To a solution of 4-chloro-2-[2-phthalimido-1-(2,3,5,6-tetrahydropyran-2-yl)oxyethyl]-7-azaindole (1 g, 2.34 mmol) in EtOH (70 mL) $NH_2NH_2.H_2O$ (1.53 mL, 5.06 mmol) was added. The mixture was refluxed for 3 h. The solvent was evaporated, the residue dissolved in CH_2Cl_2 and washed with saturated aq. $NaHCO_3$. The aqueous layer was extracted three times with CH_2Cl_2. The organic solutions were evaporated to obtain a diastereomeric mixture (1:1) of **3c** (0.67g, 98%) as a light orange solid. mp 171-172 ºC. IR (KBr) ν 3200 (NH). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50-1.90 (m, 6H, H3", H4" and H5"), 3.22 (m, 2H, H2'), 3.55 and 3.98 (2m, 2H, H6"), 4.60 and 4.90 (2m, 1H, H2") 4.90 and 4.05 (m and brt, *J* 5.6, 1H, H1'), 6.46 and 6.54 (s, 1H, H3), 7.07 and 7.10 (2d, *J* 5.4, 1H, H5), 8.19 and 8.25 (2d, *J* 5.4, 1H, H6). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.8 and 20.0 (t, C3”*), 25.1 and 25.3 (t, C4"*), 30.6 and 30.8 (t, C5"*), 45.25 and 47.13 (t, C6"), 63.1 and 63.6 (t, C2'), 73.1 and 75.1 (d, C1'), 96.0 and 96.4 (d, C2"*), 98.3 and 100.0 (d, C3), 115.8 (d, C5), 120.0 (s, C3a), 139.0 and 139.8 (s, C2), 1 42.4 and 142.5 (d, C6), 143.2 and 143.3 (s, C4**), 148.9 and 149.4 (s, C7a**). MS (CI) *m/z* 298 (7), 296 (M+1, 20), 214 (13), 212 (40), 196 (21), 194 (67), 183 (20), 181 (22), 84 (100). *M+H* calculated for $C_{14}H_{19}ClN_3O_2$: 296.1166; HRMS found: $M+H^+$ 296.1179

4-Chloro-6,7-dihydro-6-(2,3,5,6-tetrahydropyran-2-yl)-9-tosylaminopyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (5c). A solution of **4c** (1.0 g, 3.38 mmol) and DIPEA (2.1 mL, 12.3 mmol) in CH_2Cl_2 (50 mL) was slowly added to a solution of $TsNCCl_2$ (1.1 g, 6.15 mmol) in CH_2Cl_2 (50 mL). The resulting mixture was stirred for 30 min. and was washed with H_2O. The organic solution was dried and evaporated to give a crude which was purified by flash column chromatography. Elution with CH_2Cl_2 /MeOH (99/1) afforded **5c** (1.1 g, 68%) as a pale orange solid. IR (film) ν3309 (NH), 1634 (C=N), 1358 and 1134 (SO_2), 752 (C-Cl). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.20-1.80 (m, 6H, H3', H4', and H5'), 2.38 (s, 3H, Me), 3.40-4.00 (m, 4H, H6' and H7), 4.65 and 4.85 (2 brs, 1H, H2'), 5.02-5.15 (m, 1H, H6), 6.71 (brs, 1H, H5), 7.20-7.30 (m, 3H, H3 and Ts), 8.14 (d, *J* 8.0, 2H, Ts), 8.38 and 8.40 (2d, *J* 4.8, 1H, H2), 8.42 (brs, 1H, NH). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 18.7, 19.1 (t, C4'), 21.5 (q, Me), 25.2, 25.3 (t, C5'), 29.9, 30.2 (t, C3'), 43.1, 44.7 (t, C6'), 62.4, 62.5 (t, C7), 63.6 (d, C6), 95.8, 96.8 (d, C2'), 101.9, 103.2 (d, C3), 119.3 (d, C5), 120.9 (s, C5a), 126.4 (d, Ts), 129.2 (d, Ts), 132.9 (s, C4a), 136.3 (s, C9), 139.8 (s, C4), 142.6 (s, Ts), 145.8, 146.2 (d, C2), 147.8 (s, C10a).

***N*-Tritylformamide.** A mixture of Ac_2O (16.7 mL, 18.1 mmol) and HCO_2H (0.68 mL, 18.1 mmol) was stirred at 55 ºC under argon for 4 h. After this time the mixture was cooled at room temperature and the resulting solution was added to a solution of tritylamine (2.0 g, 7.7 mmol) in dry THF (6 mL) cooled at 0 ºC. The resulting mixture was stirred at rt for 20 h. After this time the solution was washed with saturated Na_2CO_3 and the organic layer was extracted with

CH_2Cl_2. The organic solution was dried and evaporated to give quantitatively a wite solid mp 120-122 ºC (lit.[13] 121-122 ºC) IR (KBr) ν3230 (NH), 1682 (C=O). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 81.3 (s), 127.6 (d), 127.7 (d), 129.6(d), 145.2 (s)., 166 (s).

***N*-Tritydichloromethanimine (3c).** To a mixture of SO_2Cl_2 (0.3 mL, 3.5 mmol) and $SOCl_2$ (1.1 mL) cooled at 15 ºC was slowly added *N*-tritylformamide (1 g, 3.5 mmol) and the reaction mixture was stirred at the same temperature for 30 min and after this time at 80 ºC during 2h. The excess of reagents were eliminated under vacuum to leave a yellow solid (1.01g, 86%) which was used without further purification. ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 81.3 (s, CCl_2), 127.6 (s, Ar), 127.8 (s, Ar), 129.6 (s, Ar), 145.2 (s, Ar). MS (CI) 341 (M+1, 0.1), 288 (2), 260 (6), 243 (100), 183 (24), 165 (87), 105 (53), 77 (45).

6,7-Dihydro-6-(2,3,5,6-tetrahydropyran-2-yl)oxy-9-tritylaminopyrido[3´,2´:4,5]pyrrolo[1,2-c]pyrimidine (7a). A solution of **3c** (0.75 g, 2.2 mmol) in dry CH_2Cl_2 (50 mL) was added over a solution of **4a** (0.48 g, 1.8 mmol) and DIPEA (4.6 mmol) in dry CH_2Cl_2 (25 mL) and the mixture was stirred at rt for 1 h. After this time the resulting solution was washed with brine and dried. The solvent was eliminated and the residue was purified by column chromatography. Elution with CH_2Cl_2/MeOH 95:0.5 gave the (6RS,2'SR)**7a** (0.56 g, 58%) as a yellow solid. ^{1}H-NMR ($CDCl_3$, 300MHz) δ 1.40-1.90 (m, 6H, CH_2), 2.62 and 2.74 (2m, 2H, H7), 3.56 (dt, *J* 11.7 and 4.2 Hz, 1H, H6'), 3.99 (m, 1H, H6'), 4.58 (t, *J* 3.0 Hz, 1H, H2'), 5,08 (t, *J* 5.1 Hz, 1H, H6), 6.39 (s, 1H, H5), 7.02 (dd, *J* 7.8 and 4.5 Hz, 1H, H3), 7.06 (m, 9H, ArH), 7.42 (dd, *J* 8.1 and 1.5 Hz, 6H, ArH), 7.86 (dd, *J* 7.8 and 1,5 Hz, 1H, H4), 8,18 (dd, *J* 4.8 and 1.5Hz, 1H, H2), 10.68 (sa, 1H, NH). ^{13}C-NMR ($CDCl_3$, 300MHz) δ 19.3 (t, C4'), 25.4 (t, C5'), 30.4 (t, C3'), 48.9 (t, C7), 62.3 (t, C6'), 70.7 (s, C-Ar_3), 71.50 (d, C6), 77.2 (d, C2'), 95.5 (d, C4), 99.9 (d, C5), 115.7 (d, C3), 120.5 (s, C4a), 126.2 (d, Ar), 127.8 (d, Ar), 128.5 (d, Ar), 138.3 (s, C5a), 142.5 (d, C2), 145.7 (s, Ar), 148.7 (s, C10a). MS (CI) 450 (M+1-C_6H_5,16), 366 (32), 348 (25), 271 (7), 243 (trityl, 82)189 (20), 167 (49), 85 (100).

Elution with CH_2Cl_2/MeOH 98:2 afforded the (6SR, 2'SR)**7a** as an orange gum. ^{1}H-NMR ($CDCl_3$, 300MHz) δ 1.45-1.90 (m, 6H, CH_2), 2.60-2.79 (m, 2H, H7), 3.44 (m, 1H, H6'), 3.85-3.90 (m, 1H, H6'), 4.81 (dd, *J* 3.9 and 1.8, 1H, H2'), 4.99 (dd, *J* 4.5 and 4.5 Hz, 1H, H6), 6.14 (s, 1H, H5), 6.99 (dd, *J* 7.8 and 4.8 Hz, 1H, H3), 7.10-7.30 (m, 9H, ArH), 7.47 (dm, *J* 7.2, 6H, Ar), 7.80 (dd, *J* 7.8 and 1.5 Hz, 1H, H4), 8.21 (dd, *J* 4.8 and 1.5, 1H, H2), 10.18 (brs, 1H, NH). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 20.4 (t, C4'), 25.1 (t, C5'), 31.0 (t, C3'), 46.7 (t, C7), 63.9 (t, C6'), 70.7 (s, C-Ar_3), 74.2 (d, C6), 77.7 (d, C2'), 97.2 (d, C5), 100.5 (d, C4), 115.7 (d, C3), 120.5 (s, C4a), 126.2 (d, Ar), 127.8 (d, Ar), 128.5 (d, Ar), 138.9 (s, C5a), 142.5 (d, C2), 145.7 (s, Ar), 148.2 (s, C10a).

6,7-Dihydro-4-methoxy-6-(2,3,5,6-tetrahydropyran-2-yl)oxy-9-tritylaminopyrido[3´,2´:4,5] pyrrolo[1,2-*c*]pyrimidine (7b). A solution of **4b** (2.5 g, 5 mmol) and DIPEA (4.6 mL, 26.5 mmol) in CH_2Cl_2 (60 mL) was added slowly to a solution of **3c** (5.9 mg, 6.7 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred for 30 min. and was washed with H_2O. The organic solution was dried and evaporated to give a crude product which was purified by flash column chromatography. Elution with DCM: MeOH gave a diastereomeric mixture (8:2) of **7b**

(3.1 g, 64%) as a yellow solid was obtained. Mp (acetone) 132-136 ºC. IR (KBr): ν 3590 (NH), 1590, 1330. ^{1}H-NMR ($CDCl_3$, 300MHz) δ1.2-2.0 (m, 6H, H3', H4' and H6'), 2.45-2.80 (m, 2H, H7), 3.30-3.45 (m, 1H, H6'), 3.78-4.10 (m, 1H, H6'), 3.95 and 3.99 (2s, 3H, OCH_3), 4.58 and 4.82 (t and d, 1H, H2'), 4.95 and 5.06 (2dd, *J* 6.8 and 4.8 *J* 6.4 and 5.2 Hz 1H, H6), 6.23 and 6.46 (2s, 1H, H5), 7.02-7.50 (m, 16H, H3 and ArH), 8.08 and 8.11 (2d, *J* 5.0 and 5.6 Hz, 1H, H2). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ20.2 (t, C4'), 25.2 (t, C5'), 31.0 (t, C3'), 46.9 (t, C7), 55.4 (q, Me), 63.7 (t, C6'), 70.2 (s, $NCAr_3$), 74.2 (d, C2'), 94.6 (d, C6), 96.0 (s, C4a), 97.7 (d, C3), 100.2 (d, C5), 110.1 (s, 5a), 126.2 (s, C4), 126.3 (d, Ar), 127.9 (d, Ar), 128.5 (d, Ar), 136.5 (s, C5a), 144.5 (d, C10a), 145.8 (s, Ar), 150.0 (s, C), 159.8 (s, C10a). MS (CI) 310 (2), 271 (11), 262 (26), 243 (trityl, 100), 190 (13), 176 (29), 167 (39); 85(37)

4-Chloro-6,7-dihydro-6-hydroxy-9-tosylaminopyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine (8c). To a solution of **5c** (1.0 g, 2.1 mmol) in CH_2Cl_2 (30 mL) HCl 4N (30 mL) was added and the mixture was stirred for 90 min. The aqueous solution was basified with aq. Na_2CO_3 until pH 9 and was then extracted with CH_2Cl_2. The organic layer dried and evaporated yielded **8c** (573 mg, 70%). IR (film) ν 3316 (s, OH), 1632 (m, C=N), 1277 (s, SO_2). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.36 (s, 3H, Me), 3.58 (dm, *J* 14.4 Hz, 1H, H7), 3.79 (dm, *J* 14.4 Hz, 1H, H7), 4.86 (sa, OH), 5.32 (ta, 1H, H6), 6.62 (s, 1H, H5), 7.04 (d, *J* 5.2 Hz, 1H, H3), 7.24 (d, *J* 8.4 Hz, 2H, Ts), 8.03 (d, *J* 8.4 Hz, 2H, Ts), 8.16 (d, *J* 5.2 Hz, 1H, H2). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.8 (q, Me), 45.8 (t, C7), 60.4 (d, C6), 101.4 (d, C5), 119.2 (d, C3), 121.4 (s), 126.5 (d, Ts), 129.3 (d, Ts), 131.0 (s), 136.5 (s), 137.4 (s), 139.3 (s), 142.8 (s), 145.2 (d, C2), 148.3 (s). MS (EI) *m/z* 392 (^{37}ClM$^+$, 1), 390 (^{35}ClM$^+$, 1), 235 (^{35}ClM-Ts, 15), 237 (^{37}ClM-Ts, 15), 181 (54). *M* calculated for $C_{17}H_{15}{}^{35}Cl\ N_4O_3S$: 390.0553; HRMS found: M^+ 390.0547.

6,7-Dihydro-6-hydroxy-9-tritylaminopyirido[3´,2´:4,5]pyrrolo[1,2-*c*]pyrimidine (9a). A solution of **6a** (286 mg, 0.54 mmol) in CH_2Cl_2 (12 mL) and HCl 4N (12 mL) was stirred for 30 min at room temperature. The aqueous solution was basified with aq. Na_2CO_3 to pH 9 and the product was extracted with CH_2Cl_2. The organic layer was dried and evaporated and the crude material was purified by column chromatography. Elution with DCM:MeOH 8:2 afforded **8a** (198 mg, 82%) as a light yellow solid. mp 83-85 ºC. IR (KBr) ν3417 (OH, NH); 1521; 1500; 1489; 1447. ^{1}H-NMR ($CDCl_3$, 300MHz) δ2.62 (dd, *J* 12.3 and 6.6, 1H, H7), 2.72 (dd, *J* 12.3 and 4.5, 1H, H7), 4.95 (dd, *J* 6.6 and 4.5, 1H, H6), 6.10 (s, 1H, H5), 7.02 (dd, *J* 7.8 and 4.8, 1H, H3), 7.10-7.32 (m, 9H, ArH), 7.43 (dm, *J* 7.0, 6H, Ar), 7.80 (dd, *J* 7.8 and 1.5, 1H, H4), 8.22 (dd, *J* 4.8 and 1.5, 1H, H2), 9.48 (sa, 1H, NH). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ49.1 (t, C7), 68.1 (d, C6), 70.5 (s, C-Ar_3), 96.6 (d, C5), 115.7 (d, C3), 126.4 (d, Ar), 127.1 (d, C4),127.8 (d, Ar), 128.5 (d, Ar), 140.6 (s, C5a), 142.1 (d, C2), 145.5 (s, Ar), 146.5 (s, C10a), 148.3 (s, C9). MS (CI) 420 (M^+-24, 1), 402 (1), 271 (8), 244(25), 243(100), 194 (2), 188(2), 167 (42), 160 (11), 148 (18).

6,7-Dihydro-6-hydroxy-4-methoxy-9-tritylaminopyrido[3´,2´:4,5]pyrrolo[1,2-c]pyrimidine (9b). A solution of **7b** (461 mg, 0.83 mmol) in CH_2Cl_2 (35 mL) HCl 4N (35 mL) was stirred for 45 min at room temperature. The aqueous solution was basified with aq. Na_2CO_3 to pH 9 and the product was extracted with CH_2Cl_2. The organic layer was dried and evaporated and the crude material was purified by column chromatography. Elution with DCM: MeOH 99:1 to 98:2

afforded **9b** (339 mg g, 87%) as a light yellow solid m.p. 194-195 ºC. IR (KBr) ν 3277 (NH/OH), 1590. ^{1}H-NMR ($CDCl_3$, 300MHz) δ2.45-2.80 (m, 2H, H7), 3.93 (s, 3H, OCH_3), 4.92 (t, *J* 4.4 Hz, 1H, H6), 6.12 (s, 1H, H5), 6.41 (d, *J* 6.0 Hz, 1H, H3), 7.10-7.23 (m, 9H, ArH), 7.24-7.44 (m, 6H, ArH), 8.02 (d, *J* 6.0 Hz, 1H, H2), 11.5 (sa, 1H, NH). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ49.2 (t, C7), 55.4 (q, Me), 68.1 (d, C6), 70.6 (s, N-C-Ar_3), 93.9 (d, C5), 97.7 (d, C3), 110.6 (s, C4a), 126.3 (d, Ar), 127.8 (d, Ar), 128.5 (d, Ar), 138.2 (s, C5a), 144.1 (d, C2), 145.6 (s, Ar), 150.0 (s, C), 159.4 (s, C10a). MS (CI) 450 (M^+-24, 2), 432 (2), 271 (11), 243 (trityl, 100), 218(3), 190 (19), 178 (7), 167 (52), 149 (6).

4-Chloro-9-tosylaminopyrido[3´,2´:4,5]pyrrolo[1,2-c]pyrimidine (10c). To a cooled solution of **8c** (165 mg, 0.4225 mmol) and TEA (0.130 mL, 0.93 mmol) in CH_2Cl_2 (200 mL) at 0 ^{o}C, MsCl (0.033 mL, 0.4648 mmol) was added dropwise. The reaction mixture was stirred for 30 min at 0 ^{o}C then the organic solution was washed with saturated aq. NH_4Cl and with water. The organic solution was dried and evaporated to give a crude material. Purification by flash column chromatography gave on elution with CH_2Cl_2/MeOH (98/2) **10c** (120 mg, 76%) as a yellow solid. ^{1}H-NMR (CD_3OD, 200 MHz) δ 2.34 (s, 3H, Me), 6.79 (s, 1H, H5), 6.84 (d, *J* 7.8 Hz, 1H, H6), 7.17 (d, *J* 7.8 Hz, 1H, H7), 7.58 (d, *J* 5.4 Hz, 1H, H3), 7.37 (d, *J* 7.8 Hz, 2H, Ar), 8.02(d, *J* 7.8 Hz, 2H, Ar), 8.44 (d, *J* 5.4 Hz, 1H, H2), 11.05 (sa, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75 MHz) δ 21.0 (q, Me), 93.7 (d, C5), 101.3(d, C6), 119.9 (d, C3), 122.5 (s), 125.9 (d, Ts), 126.3 (d, C7), 129.4 (d, Ts), 133.4 (s), 135.6 (s), 140.0 (s), 142.4 (s), 143.4 (d, C2), 143.8 (s), 145.1 (s). MS (EI) *m/z* 374 ($^{37}ClM^+$, 5), 372 ($^{35}ClM^+$, 12), 307 (64), 217 (31), 182 (36). *M* calculated for $C_{17}H_{13}{}^{35}Cl\ N_4O_2S$ 372,0447; HRMS found: M^+ 372,0444.

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References and Notes

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