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A Short Synthesis of 4-Substituted 1-(Hydroxyalkyl)-1H-pyrazolo[3,4-d]pyrimidines.†

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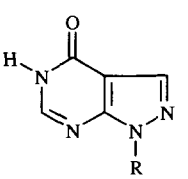
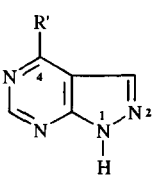
Abstract: *A simple and practical procedure was developed for the preparation of 4-substituted-1-(hydroxyalkyl)-1H-pyrazolo[3,4-d]pyrimidines. This was achieved by reacting nucleobase* ***3a*** *or* ***3b*** *with cesium carbonate or DBU in the presence of various alkyl iodides at 0°C in DMF. This procedure appears to be of general utility, proceeds in reasonable yield, and is applicable to different alkyl chain lengths including protected and unprotected alcohols. The synthetic utility of this approach is demonstrated by the facile synthesis of ST 689, a potent immunostimulatory drug.*

Pyrazolo[3,4-d]pyrimidines and their ribofuranosides are of considerable interest because of their potential therapeutic applications[1]. An example of these biologically active isomeric purine analogues is allopurinol (pyrazolo[3,4-d]pyrimidin-4-one); **1**. This compound inhibits xanthine oxidase[2] and subsequently is used for the treatment of hyperuracemia and gouty arthritis[3]. A derivative of allopurinol, ST 689 (1,5-dihydro-1-(5-hydroxypentyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one; **2**), has been recently reported to possess promising antitumor properties[4]. This activity arises from the ability of ST 689 to act as an immunostimulant (affecting T-cells, macrophages and NK cells)[5].



	R
1	-H
2	-$(CH_2)_5$-OH



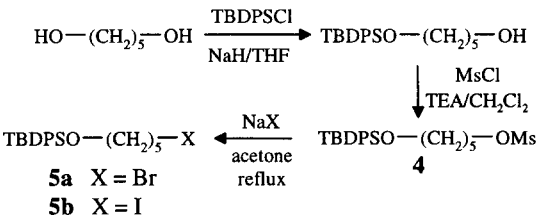
	R'
3a	-Cl
3b	-OCH_3

As part of our immunomodulator research program, we identified a small synthetic non-toxic immunostimulatory molecule, BCH-1393[6]. This compound inhibits tumor growth *in vivo*, and has an immunological profile similar to ST 689; **2**. Thus, compound **2** was required for comparative studies. The preparation is described in the literature[4]. However, it involves a multi-step synthesis, with hygroscopic

intermediates, and the overall yield is low. We therefore developed a short and general route for the preparation of alkyl pyrazolo[3,4-d]pyrimidines and in particular a regioselective procedure for **2**.

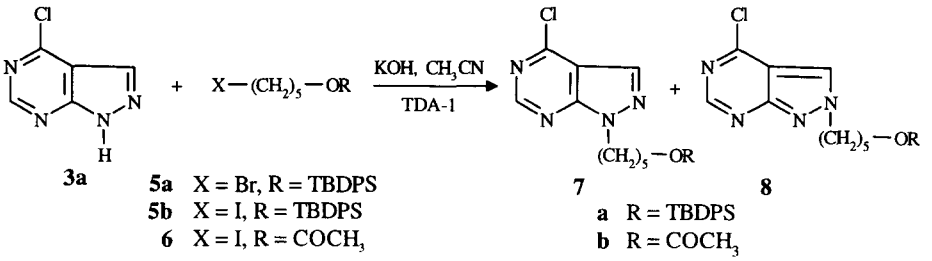
Few reactions for the short chain alkylation of pyrazolo[3,4-d]pyrimidines are available[7]. The general procedure requires treatment of the pyrimidine reactant with a large excess of alkyl halide. This proceeds in a biphasic mixture (dichloromethane or benzene and 50% aqueous sodium hydroxide), in the presence of a high mole percent concentration of a phase-transfer catalyst. This procedure is limited by the solubility of the pyrimidine anion in organic solvents and the reaction requires thorough mixing with a vibromixer. Therefore, it was decided to explore a more practical approach, as suggested by the recently reported glycosylation of the anion of **3b** with arabinofuranosyl chloride[8] (powdered KOH; 0.1 mole % TDA-1, tris[2-(2-methoxy-ethoxy)ethyl]amine, as phase-transfer catalyst; CH_3CN).

Previous work has demonstrated that allopurinol **1** is not appropriate for N-1 alkylation due to the nucleophilicity of the lactam portion of the pyrimidine ring[7a]. We selected 4-chloro-1H-pyrazolo[3,4-d]-pyrimidine **3a** as the key base intermediate, since 4-halo-substituents are useful for derivitization at the 4-position. Precursor **3a** is commercially available[9] or conveniently prepared by chlorination of allopurinol **1**[10]. We therefore investigated the reaction between **3a** and protected alkyl halides **5a** or **5b**. The latter were prepared according to scheme 1 starting from 1,5-pentanediol.



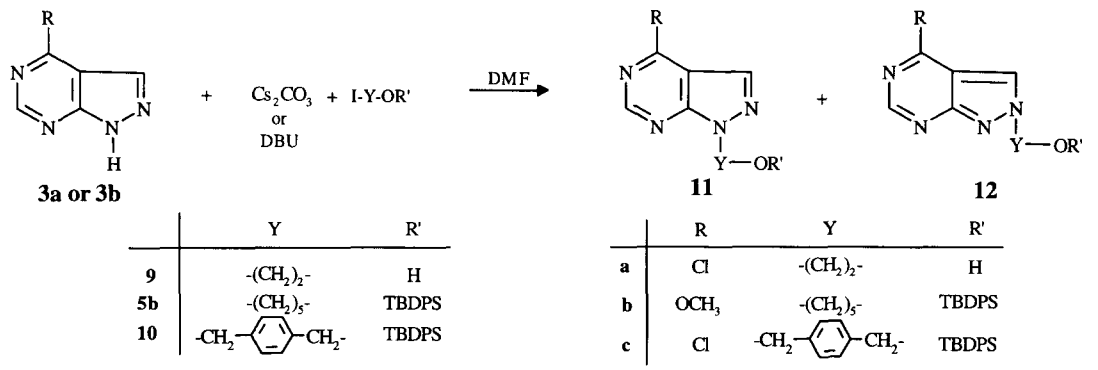
Scheme 1

Alkylation of **3a** with bromosilyl ether **5a** according to the procedure reported for glycosylation of **3b**[8] (acetonitrile using excess powdered KOH and TDA-1 as catalyst; scheme 2) proceeded in very low yield. Heating the mixture gave decomposition of the reactants. If iodide **5b** was used instead of bromide **5a**, the N-1 alkylated product **7a** was isolated in 17% yield. However, replacing powdered KOH with pellets increased the product yield. This afforded regioselectively the N-1 chloroderivative **7a** as the main product (26% yield) together with the N-2 isomer **8a** (10% yield). The two isomers are readily separated by silica gel chromatography, with elution of the less polar N-1 isomer prior to the N-2 isomer. Similar results were also obtained starting with 5-iodopentyl acetate **6**[11]. The low yield obtained during the alkylation step may arise from the relative lability of base **3a** in the presence of a phase-transfer catalyst. The latter was reported[12, 7c] to generate side reactions with the reactive halogen present in **3a** under standard glycosylation conditions.



Scheme 2

In an attempt to improve yields, we examined homogeneous alkylation reaction conditions. Evaluation of a number of bases and solvents was undertaken. The sodium salt of **3a**[13], prepared *in situ* by treatment with NaH in acetonitrile, was treated with mesylate **4** or bromide **5a** at 50°C. Only traces of the expected product **7a** were produced. However, if iodide **5b** was used, a slow reaction was observed although the yield of the product was low. Further investigation revealed that treatment of base **3a** with cesium carbonate or DBU followed by alkylation with iodide **5b** in dry DMF at 0°C gave the N-1 isomer **7a** in 52% yield and N-2 isomer **8a** in 20% yield (scheme 3). The reaction is rapid and clean. Similarly, iodide **6** gave comparable yields under the same conditions. Increasing the temperature to 25°C accelerates the formation of side products at the expense of the desired product. This is not surprising since the highly reactive chlorine at the 4-position is susceptible to hydrolysis in polar solvents[12a, 7b]. Changing the solvent from DMF to 1,2-dimethoxyethane affects the rate considerably and lowers the yield, presumably due to the lower solubility of the anion of **3a** in the latter solvent. However, if the methoxy derivative **3b**[7b] was used instead of base **3a**, the yield of alkylated products was almost quantitative. Our results are summarized in table 1. Best yields are obtained using cesium carbonate, alkyl iodide and DMF as solvent at 0°C. The procedure is general for different alkyl chain lengths and is applicable to protected and unprotected alcohols.

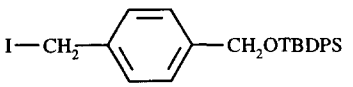


	Y	R'
9	-$(CH_2)_2$-	H
5b	-$(CH_2)_5$-	TBDPS
10	-CH_2-C$_6$H$_4$-CH_2-	TBDPS

	R	Y	R'
a	Cl	-$(CH_2)_2$-	H
b	OCH_3	-$(CH_2)_5$-	TBDPS
c	Cl	-CH_2-C$_6$H$_4$-CH_2-	TBDPS

Scheme 3

Table 1. Percent Yields of N-1 and N-2 Isomers.

Alkyl iodide	Base	Nucleobase	N-1	(%)	N-2	(%)
I-$(CH_2)_2$-OH	Cs_2CO_3	3a	11a[14]	46	12a[15]	14
I-$(CH_2)_5$-OTBDPS	Cs_2CO_3	3a	7a	52	8a	20
I-$(CH_2)_5$-OTBDPS	DBU	3a	7a	48	8a	15
I-$(CH_2)_5$-$OCOCH_3$	Cs_2CO_3	3a	7b	50	8b	17
	Cs_2CO_3	3a	11c	49	12c	15
I-$(CH_2)_5$-OTBDPS	Cs_2CO_3	3b	11b	76	12b	22
I-$(CH_2)_5$-OTBDPS	DBU	3b	11b	75	12b	20

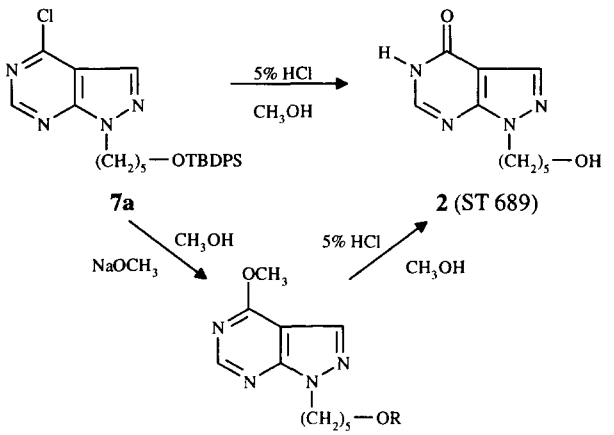
The structural assignment of the isomers was determined by ^1H and ^{13}C NMR spectroscopy. The N-1 compounds **7a**, **7b**, **11a**, **11b** and **11c** give ca. 7-10 ppm upfield shifts of C-3 and similar downfield shifts of C-7a relative to the N-2 isomers **8a**, **8b**, **12b** and **12c** (Table 2). This pattern is similar to that observed for N-1 and N-2 methyl-4-methoxy-1H-pyrazolo[3,4-d]pyrimidine[7a]. Further evidence to confirm the assigned structure is based on the proton-coupled ^{13}C NMR spectra. For example, C-3 of the N-1 isomer of **7b** shows only a large ^1J (CH) coupling with H-3. An additional ^3J (CH) coupling of C-3 with the protons of the methylene group [^3J C-3, CH_2] was observed in the spectrum of N-2 isomers **8b**, indicating alkylation at N-2. The spectrum of N-1 also shows a complex multiplet for C-7a due to three ^3J (CH) couplings with H-3, H-6, and CH_2-N whereas the C-7a signal of N-2 exhibits only two defined coupling constants with H-6 and H-3. These findings are in agreement with values reported in the literature for N-1 and N-2 methyl-4-methoxy-1H-pyrazolo[3,4-d]pyrimidine[7a]. Additional structural information was obtained from HMBC and HMQC (Heteronuclear Multiple Bond (or Quantum) Coherence) experiments. This data confirms the assignment of H-3 and H-6, as well as the chemical shifts of the aliphatic methylene side chain CH_2-N and CH_2-O.

Table 2. ^{13}C Chemical Shifts of Pyrazolo[3,4-d]pyrimidines δ(ppm).[a]

Carbon	2	3a	7a	7b	8a	8b	11a	11b	11c	12b	12c
C-3	136.0	130.6	130.9	131.0	123.0	123.0	131.4	129.8	133.2	123.7	122.9
C-3a	107.6	101.0	112.7	112.7	112.1	112.2	112.9	101.3	112.9	101.8	112.5
C-4	160.8	163.4	153.8	153.9	155.3	155.3	154.2	163.2	153.9	164.7	155.5
C-6	149.0	154.2	153.4	153.5	153.8	153.9	153.6	153.3	153.8	154.1	153.9
C-7a	154.0	155.0	152.1	152.1	158.9	158.9	152.4	154.0	152.2	159.8	158.9
CH_2-O	63.2		62.5	63.1	62.3	62.9	60.3	62.2	64.2	62.1	64.1
CH_2-N	b		46.9	46.6	54.1	53.9	49.9	47.3	50.4	52.6	57.7
2'-CH_2	33.5		31.0	28.1	30.8	28.9		30.6		30.6	
3'-CH_2	24.5		22.0	22.1	21.9	22.1		21.6		21.5	
4'-CH_2	31.0		28.3	27.1	28.8	27.0		28.0		28.5	
OCH_3		52.5						52.6		52.6	
$\underline{C}Me_3$			25.9		25.9			24.9	5.9	24.9	25.9
$\underline{C}Me_3$			18.2		18.2			17.6	18.4	17.6	18.4

[a] All spectra were obtained in $CDCl_3$, except **2**, **3a**, **11b**, and **12b** (CD_3OD). [b] Obscured by solvent.

To our knowledge, this is the first example where the pyrazolopyrimidine anion is generated from cesium carbonate or DBU in DMF. This salt, under homogeneous conditions, reacts efficiently with alkyl iodides to give regioselectively the most thermodynamically stable, N-1 alkylated, products. The ratio of N-1 to N-2 isomers remains constant at 3:1 in all reactions.



11

11b R = OTBDPS
11d R = H

Scheme 4

This approach was applied to the synthesis of ST 689; **2**. Chloro **7a** was converted in a single step to ST 689 using 5% HCl in methanol (scheme 4). These conditions resulted in the simultaneous hydrolysis of the chloro function and removal of the silyl protecting group. It is likely that the intermediate in this reaction is the methoxy derivative **11d** which was formed during the hydrolysis of chloro **7a**. Indeed, acidic cleavage of the methoxy group of **11b** with 5% HCl in methanol gave the intermediate **11d** which was converted in a few hours to the expected product **2** (scheme 4). This result may represent an alternative route for the preparation of ST 689, in three steps in high yield starting from chloro **3a**. For example, treatment of the nucleobase **3a** with sodium methoxide affords the methoxy **3b**[7a] which is alkylated to give **11d**. The latter is hydrolyzed under the same conditions to afford compound **2**. The melting point, ^{1}H, ^{13}C NMR and mass spectral data for the ST 689 product were in agreement with that reported in the literature[4].

In conclusion, a new, practical and general procedure for the preparation of 4-substituted 1-(hydroxyalkyl)-1H-pyrazolo[3,4-d]pyrimidines is described herein. This alkylation method proceeds in good yield, overcomes many of the limitations previously reported for the preparation of haloheterocyclic derivatives, and is therefore superior to the literature methods. The potential utility of this approach has been illustrated by the facile synthesis of the immunostimulant ST 689. This approach is expected to be applicable to nucleosides containing different fused heterocyclic pyrimidine rings. Investigations towards the synthesis of such nucleosides are in progress.

EXPERIMENTAL SECTION

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. TLC was performed on silica gel GOF_{254} plates with solvent systems; A) 30% EtOAc-hexanes; B) 50% EtOAc-hexanes; C) EtOAc; D) 15% MeOH-EtOAc. UV spectra were recorded on a Varian Cary 1 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker DRX-400 or on a Varian VXR-300 spectrometer. Mass spectra were recorded on a Kratos MS-50 TA instrument. All reagents were obtained from Aldrich Chemical Co. (Milwaukee WI) except for nucleobase **3a**[9,10] and **3b**[7a].

General Procedure for the Preparation of tert-Butyldiphenyl-(iodoalkyloxy)-silanes

To a solution of diol (30 mmol) in THF (50 mL) under nitrogen was added sodium hydride (dry, 33 mmol), and the mixture was stirred at rt. After 30 min, a solution of *tert*-butylchlorodiphenylsilane (30 mmol) in THF (50 mL) was added dropwise, and the stirring was continued for 4 h. To the mixture was added a 10% solution of potassium carbonate (100 mL), followed by extraction with ether. The combined extracts were dried ($MgSO_4$), and concentrated to give an oil. This was then purified by silica gel column chromatography to give the mono-protected alcohol. To the alcohol (14.5 mmol) dissolved in CH_2Cl_2 (100 mL) under nitrogen and cooled (0°C) was added triethylamine (29 mmol), followed by MsCl (22 mmol). After 1 h, saturated ammonium chloride (100 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give an oily solid, which was then dissolved in acetone. To this was added NaI (44.6 mmol), and the solution was heated at reflux for 16 h. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography to give the product.

tert-Butyldiphenyl-(5-iodopentyloxy)-silane (5b). Colorless oil; ^1H NMR ($CDCl_3$) δ 7.81 (m, 4H, aromatic), 7.51 (m, 6H, aromatic), 3.81 (t, 2H, CH_2-O, J = 6 Hz), 3.28 (t, 2H, CH_2-I, J = 7 Hz), 2.06 (p, 2H, CH_2, J = 7 Hz), 1.79 (p, 2H, CH_2, J = 6 Hz), 1.19 (s, 9H, *t*-Bu).

tert-Butyldiphenyl-(4-iodomethylbenzyloxy)-silane (10). Colorless oil; ^1H NMR ($CDCl_3$) δ 7.79 (d, 4H, aromatic), 7.53-7.35 (m, 10H, aromatic), 4.83 (s, 2H, CH_2), 4.53 (s, 2H, CH_2), 1.21 (s, 9H, *t*-Bu).

General procedure for the preparation of 4-substituted 1-(hydroxyalkyl)-1H-pyrazolo[3,4-d]-pyrimidines

Cesium carbonate or DBU (1.1 mmol) was added to a solution of **3a** or **3b** (1 mmol) in dry DMF (5 ml) at 0°C. To this suspension, alkyl iodide (1.2 mmol) was added and the reaction mixture was stirred at this temperature for three hours. Insolubles were removed by filtration and washed with CH_2Cl_2 (2 x 5 ml). Solvent was then evaporated under reduced pressure and the residue was purified by silica gel column chromatography using an EtOAc-hexanes gradient. Appropriate fractions were combined to give the expected N-1 and N-2 products.

1-[5-(tert-Butyldiphenylsilyl)oxypentyl]-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (7a). Colorless oil; TLC (A) R_f = 0.75; UV (MeOH) λ_{max} 260 nm (ε 4200); ^1H NMR ($CDCl_3$) δ 8.75 (s, 1H, H-6), 8.15 (s, 1H, H-3), 7.62 (m, 4H, aromatic), 7.42-7.34 (m, 6H, aromatic), 4.50 (t, 2H, CH_2-N, J = 7 Hz), 3.63 (t, 2H, CH_2-O, J = 6 Hz), 2.01-1.92 (m, 2H, CH_2), 1.64-1.56 (m, 2H, CH_2), 1.42-1.34 (m, 2H, CH_2), 1.00 (s, 9H, *t*-Bu); LRMS (FAB) m/z = 479 (MH^+); HRMS calcd for $C_{26}H_{32}N_4OSiCl$ (MH^+) 479.2034, found 479.2015.

2-[5-(tert-Butyldiphenylsilyl)oxypentyl]-4-chloro-2H-pyrazolo[3,4-d]pyrimidine (8a). Colorless oil; TLC (A) R_f = 0.35; UV (MeOH) λ_{max} 259 nm (ε 3600); ^1H NMR ($CDCl_3$) δ 8.85 (s, 1H, H-6), 8.08 (s, 1H, H-3), 7.65 (m, 4H, aromatic), 7.42-7.34 (m, 6H, aromatic), 4.44 (t, 2H, CH_2-N, J = 7 Hz), 3.66 (t, 2H, CH_2-O,

J = 6 Hz), 2.10-2.00 (m, 2H, CH_2), 1.60-1.51 (m, 2H, CH_2), 1.45-1.37 (m, 2H, CH_2), 1.01 (s, 9H, *t*-Bu); LRMS (FAB) m/z = 479 (MH^+); HRMS calcd for $C_{26}H_{32}N_4OSiCl$ (MH^+) 479.2034, found 479.2049.

1-[5-Acetoxypentyl]-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (7b). Colorless oil; TLC (A) R_f =0.55; UV (MeOH) λ_{max} 260 nm (ε 4100); ^1H NMR ($CDCl_3$) δ 8.70 (s, 1H, H-6), 8.10 (s, 1H, H-3), 4.56 (t, 2H, CH_2N, J = 7 Hz), 3.97 (t, 2H, CH_2-O, J = 6.5 Hz), 1.96 (s, 3H, CH_3), 2.02-1.88 (m, 2H, CH_2), 1.758-1.57 (m, 2H, CH_2), 1.36-1.29 (m, 2H, CH_2); LRMS (FAB) m/z = 283 (MH^+); HRMS calcd for $C_{12}H_{16}N_4O_2Cl$ (MH^+) 283.0962, found 283.0972.

2-[5-Acetoxypentyl]-4-chloro-2H-pyrazolo[3,4-d]pyrimidine (8b). m.p. 30 °C; TLC (C) R_f = 0.11; UV (MeOH) λ_{max} 259 nm (ε 3800); ^1H NMR ($CDCl_3$) δ 8.80 (s, 1H, H-6), 8.17 (s, 1H, H-3), 4.50 (t, 2H, CH_2N, J = 7 Hz), 4.07 (t, 2H, CH_2-O, J = 6.5 Hz), 2.20-2.09 (m, 2H, CH_2), 2.04 (s, 3H, CH_3), 1.80-1.69 (m, 2H, CH_2), 1.50-1.38 (m, 2H, CH_2); LRMS (FAB) m/z = 283 (MH^+); HRMS calcd for $C_{12}H_{16}N_4O_2Cl$ (MH^+) 283.0962, found 283.0972.

4-Chloro-1-[2-hydroxyethyl]-1H-pyrazolo[3,4-d]pyrimidine (11a). m.p. 93-94 °C (lit.[14] m.p. 93-95 °C); TLC (A) R_f = 0.37; UV (MeOH) λ_{max} 259 nm (ε 4100); ^1H NMR ($CDCl_3$) δ 8.75 (s, 1H, H-6), 8.16 (s, 1H, H-3), 4.64 (t, 2H, CH_2-N, J = 5 Hz), 4.12 (t, 2H, CH_2-O, J = 5 Hz), 3.04 (bs, 1H, OH); LRMS (FAB) m/z = 199 (MH^+); HRMS calcd for $C_7H_8N_4OCl$ (MH^+) 199.0387, found 199.0395.

4-Chloro-2-[2-hydroxyethyl]-2H-pyrazolo[3,4-d]pyrimidine (12a)[15]. White solid (unstable); TLC (C) R_f = 0.22; ^1H NMR ($CDCl_3$) δ 8.79 (s, 1H, H-6), 8.19 (s, 1H, H-3), 4.56 (t, 2H, CH_2-N, J = 5 Hz), 4.16 (t, 2H, CH_2-O, J = 5 Hz); LRMS (FAB) m/z = 199 (MH^+).

1-[5-(tert-Butyldiphenylsilyl)oxypentyl]-4-methoxy-1H-pyrazolo[3,4-d]pyrimidine (11b). Colorless oil; TLC (A) R_f = 0.50; UV (MeOH) λ_{max} 246, 264 nm (sh) (ε 5400, 3700); ^1H NMR (CD_3OD) δ 8.48 (s, 1H, H-6), 8.04 (s, 1H, H-3), 7.55 (m, 4H, aromatic), 7.36-7.22 (m, 6H, aromatic), 4.40 (t, 2H, CH_2-N, J = 6.5 Hz), 4.11 (s, 3H, O-CH_3), 3.57 (t, 2H, CH_2-O, J = 6 Hz), 1.90-1.80 (m, 2H, CH_2), 1.54-1.43 (m, 2H, CH_2), 1.38-1.30 (m, 2H, CH_2), 0.91 (s, 9H, *t*-Bu); LRMS (FAB) m/z = 475 (MH^+); HRMS calcd for $C_{27}H_{35}N_4O_2Si$ (MH^+) 475.2529, found 475.2521.

2-[5-(tert-Butyldiphenylsilyl)oxypentyl]-4-methoxy-2H-pyrazolo[3,4-d]pyrimidine (12b). Colorless oil; TLC (C) R_f = 0.45; UV (MeOH) λ_{max} 261 nm (ε 7300); ^1H NMR (CD_3OD) δ 8.48 (s, 1H, H-6), 8.04 (s, 1H, H-3), 7.60 (m, 4H, aromatic), 7.48-7.28 (m, 6H, aromatic), 4.40 (t, 2H, CH_2-N, J = 6.5 Hz), 4.11 (s, 3H, O-CH_3), 3.57 (t, 2H, CH_2-O, J = 6 Hz), 1.98-1.90 (m, 2H, CH_2), 1.65-1.58 (m, 2H, CH_2), 1.42-1.30 (m, 2H, CH_2), 0.91 (s, 9H, *t*-Bu); LRMS (FAB) m/z = 475 (MH^+); HRMS calcd for $C_{27}H_{35}N_4O_2Si$ (MH^+) 475.2529, found 475.2522.

1-[4-(tert-Butyldiphenylsilyloxymethyl)benzyl]-4-chloro-1H-pyrazolo[3,4-d]pyrimidine (11c).
Colorless oil; TLC (A) R_f = 0.62; UV (MeOH) λ_{max} 254, 323 nm (ε 8200, 4500); ^1H NMR ($CDCl_3$) δ 8.83 (s, 1H, H-6), 8.19 (s, 1H, H-3), 7.72 (m, 6H, aromatic), 7.50-7.36 (m, 8H, aromatic), 5.69 (s, 2H, CH_2), 4.77 (s, 2H, CH_2), 1.11 (s, 9H, *t*-Bu); LRMS (FAB) m/z = 514 (MH^+); HRMS calcd for $C_{29}H_{30}N_4OSiCl$ (MH^+) 513.1877, found 513.1897.

2-[4-(tert-Butyldiphenylsilyloxymethyl)benzyl]-4-chloro-2H-pyrazolo[3,4-d]pyrimidine (12c).
Colorless oil; TLC (C) R_f = 0.16; UV (MeOH) λ_{max} 253, 324 nm (ε 7700, 4400); ^1H NMR ($CDCl_3$) δ 8.86 (s, 1H, H-6), 8.04 (s, 1H, H-3), 7.70 (m, 6H, aromatic), 7.46-7.28 (m, 8H, aromatic), 5.64 (s, 2H, CH_2), 4.79 (s, 2H, CH_2), 1.10 (s, 9H, *t*-Bu); LRMS (FAB) m/z = 514 (MH^+).

Synthesis of 1,5-Dihydro-1-(5-hydroxypentyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one, ST 689 (2)

A solution of **7a** (0.100 g, 0.2 mmol) in 5% HCl-methanol solution (15 ml) was stirred at room temperature for 4 hours. Solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography to give ST 689, **2** (41 mg, 92%) as a white powder; m.p. 183-184 °C (lit.[4] m.p. 183-184 °C); TLC (D) R_f = 0.30; UV (MeOH) λ_{max} 252 nm (ε 6300); ^{1}H NMR (CD_3OD) δ 7.85 (s, 1H, H-6), 7.81 (s, 1H, H-3), 4.16 (t, 2H, CH_2-N, J = 7 Hz), 3.30 (t, 2H, CH_2-O, J = 6.5 Hz), 1.74-1.65 (m, 2H, CH_2), 1.39-1.30 (m, 2H, CH_2), 1.16-1.06 (m, 2H, CH_2), LRMS (FAB) m/z = 223 (MH^+); HRMS calcd for $C_{10}H_{15}N_4O_2$ (MH^+) 223.1195, found 223.1185.

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REFERENCES AND NOTES

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1. (a) Nelson, D.J., LaFon, S.W., Tuttle, J.V., Miller, W.H., Krenitsky, T.A., Elion, G.B., Berens, R.L., Marr, J.J. *J. Biol. Chem.* **1979**, 254, 11544. (b) Berens, R.L., Marr, J.J., Nelson, D.J., LaFon, S.W. *Biochem. Pharmacol.* **1980**, 29, 2397. (c) Cottam, H.B., Petrie, C.R., McKernan, P.A., Goebel, R.J., Kent Dalley, N., Davidson, R.B., Robins, R.K., Revankar, G.R. *J. Med. Chem.* **1984**, 27, 1119. (d) Oertel, F., Winter, H., Kazimierczuk, Z., Richter, P., Seela, F. *Liebigs Ann. Chem.* **1992**, 1165.
2. (a)Massey, V., Komai, H., Palmer, G., Elion, G.B. *J. Biol. Chem.* **1970**, 245, 2837. (b)Robins, R. K., Revankar, G. R., O'Brien, D. E., Springer, R. H., Novinson, T., Albert, A., Senga, K., Miller, J. P., Streeter, D., G. *J. Heterocyclic Chem.* **1985**, 22, 601
3. (a) Elion, G.B., Callahan, S.W., Nathan, H., Bieber, S., Rundles, R.W., Hitchings, G.H. *Biochem. Pharmacol.* **1963**, 12, 85. (b) Goldfinger, S.E. *New Eng. J. Med.* **1971**, 285, 1303.
4. Marzi, M., Minetti, P. U.S. patent 93/5272151.
5. De Simone, C., Famularo, G., Foresta, P., Albertoni, C., Martelli, E.A. *Ann. N. Y. Acad. Sci.* **1993**, 685, 344.
6. Zacharie, B., Connolly, T., Attardo, G., Gagnon, L., St-Denis, Y., Penney, C. U.S. patent pending.
7. (a) Rosemeyer, H., Kaiser, K., Seela, F. *J. Org. Chem.* **1985**, 50, 1847. (b) Seela, F., Steker, H. *Helv. Chim. Acta.* **1985**, 68, 563. (c) Seela, F., Steker, H. *Heterocycles* **1985**, 23, 2521.
8. Seela, F., Winter, H., Möller, M. *Helv. Chim. Acta* **1993**, 76, 1450; and references cited therein.
9. Omega Chemical Company Inc., Lévis, Québec, Canada.
10. Robins, R.K. *J. Am. Chem. Soc.* **1956**, 78, 784.
11. Prepared as described in: (a) Oku, A., Harada, T., Kita, K. *Tetrahedron Lett.* **1982**, 23, 681. (b) Forth, M.A., Smith, S. *Synthetic Communications* **1994**, 24, 951.
12. (a) Seela, F., Steker, H. *J. Chem. Soc. Perkin Trans. I* **1985**, 2573. (b) Seela, F., Westermann, B., Bindig, U. *J. Chem. Soc. Perkin Trans. I* **1988**, 697.
13. Kazimierczuk, Z., Cottam, H.B., Revankar, G.R., Robins, R.K. *J. Am. Chem. Soc.* **1984**, 106, 6379.
14. This compound was reported in the literature Chem. Abstr., **1987**, 168097.
15. This compound is unstable on standing. Only ^{1}H NMR and LRMS spectra were obtained.

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