Synthesis of 5-arylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-ones

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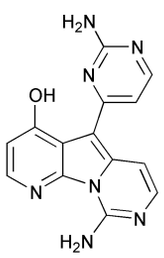
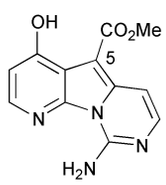
The preparation of several 2-substituted 5-arylpyrrolo[1,2-*c*]pyrimidinones **6** is described *via* palladium(0)-catalyzed couplings using 5-trimethylstannylpyrrolopyrimidinones **3**.

Introduction

The variolins (variolins B and D are typical) from the Antarctic sponge *Kirkpatrickia varialosa*,[1] are a group of marine alkaloids having as a common structural feature a 5-substituted pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine. These substances have been shown to be active against P388 murine leukemia cells.[1a] *In vitro*, variolin B was the most active in tests for antiviral activity (*Herpes simplex* Type I, *polio* Type I). Variolin D, with a methoxycarbonyl group at C-5 instead of a substituted pyrimidine, was not active. Several tricyclic synthetic analogues of the alkaloids have been reported[2a–e] and recently an elegant total synthesis of variolin B has been reported.[2f]



variolin B

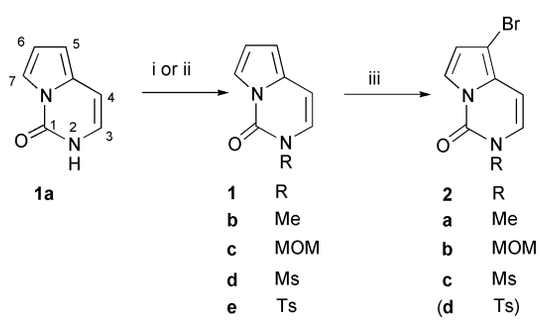


variolin D

In a previous paper[3] we described the preparation of simplified structural analogues of the variolins, lacking the pyrimidine ring, using the Stille reaction between 3-trimethylstannyl-7-azaindoles and aromatic halides. None of the 3-aryl-7-azaindoles thus prepared showed activities against the usual tumor cell lines (P-388, A-549, HT-20, and MEL-28). To extend our studies of simplified analogues of the variolins, looking to locate a molecular fragment which would retain activity, we have prepared a new series of compounds, related to the variolins, but lacking the pyridine ring of the natural compounds. In our previous work[2e] we used a pyrimidin-2-one as a precursor of the 2-aminopyrimidine C ring, a similar strategy was used in the present work. Only two precedents[4] have been described for the preparation of pyrrolo[1,2-*c*]pyrimidines, however the transformation of pyrimidin-2-ones into 2-aminopyrimidines is well known.[5] One example of the transformation of a substituted pyrrolo[1,2-*c*]pyrimidin-1-one into a 1-aminopyrrolo[1,2-*c*]pyridine has been described.[6] The pyrrolo[1,2-*c*]-pyrimidin-1-one unit is contained in several synthetic compounds such as 5*H*-indolo[1,2-*c*]quinazolin-6-ones[7] and 6*H*-pyrrolo[1,2-*c*]quinazolin-5-ones.[8] This paper describes the synthesis of 5-arylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-ones, as simplified variolins, for biological testing. In previous work[9] we demonstrated the regioselective metallation of pyrrolopyrimidinone **1b** at C-7 and easy halogen–metal interchange on 5-bromo-2-methyl derivative **2a**.

Results and discussion

As in our studies of 7-azaindoles,[3] the Stille reaction[10] was chosen rather than alternative coupling regimes, because of the ease of purification of tin intermediates. *N*-Protection of pyrimidinone **1a** using iodomethane or methoxymethyl chloride (MOMCl) in THF with sodium hydride as a base at room temperature gave good yields of *N*-alkyl compounds **1b** and **1c**. Similar conditions, or even warming to 50 °C, using *tert*-butyldimethylsilyl chloride (TBDMSCl), did not give an *N*-silyl derivative. Mesyl chloride and tosyl chloride were used as sulfonylating agents with triethylamine (TEA) as base in dichloromethane at room temperature, giving **1d** and **1e**



1a

1	R	**2**	R
b	Me	**a**	Me
c	MOM	**b**	MOM
d	Ms	**c**	Ms
e	Ts	(**d**	Ts)

Scheme 1 *Reagents*: i, MeI or MOMCl, NaH, THF, rt; ii, MsCl or TsCl, TEA, CH_2Cl_2, rt; iii, NBS, CH_2Cl_2 or $CHCl_3$, rt.

(Scheme 1). ^{1}H-NMR analysis was used to establish N-2 substitution in **1b**–**e**, the ABX system of the pyrimidinone protons characteristic of **1a**, having changed to an AB system with $J^{3,4}$ between 7.5 and 8.1 Hz.

Bromination of **1b**–**e** with *N*-bromosuccinimide proceeded regioselectively at C-5 in all cases, however the yields in the brominations were strongly dependent on the protecting group. Excellent yields were obtained from the *N*-alkylated derivatives **1b** and **1c**, giving **2a** and **2b** respectively, but from **1d** only 25% of the bromo-compound **2c** was obtained, and no **2d** could be isolated, though formation of the presumably unstable bromo-derivative **2d** from **1e** was indicated by TLC analysis (Scheme 1). The regiochemistry of bromination was confirmed by examination of the ^{1}H-NMR signals from the remaining four ring protons. Here, two AB systems, with $J^{3,4}$ between 7.6 and 8.0 Hz for the six-membered ring protons and $J^{6,7}$ of 3.3 to 3.4 Hz for the five-membered ring protons characterised the bromo-derivatives.

The tin derivatives **3** were obtained from the bromo-compounds **2** by exchange reactions using *n*-BuLi at low temperature then reaction of the lithium derivative with trimethyltin chloride. Application of these conditions to **2a** gave a

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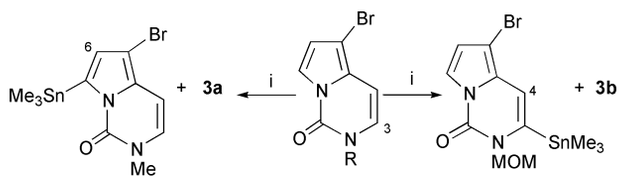
Table 1 Palladium (0)-catalysed coupling of stannanes **3a/b** with aryl/heteroaryl halides

Entry	R	Ar[a]	X	Catalyst	Compound	Yield (%)
1	Me	B	I	$Pd(PPh_3)_4$	**6a**	40
2	MOM	B	Br	$Pd(PPh_3)_4$	**6b**	17
3	MOM	C	Br	$Pd(PPh_3)_4$	**6c**	63
4	MOM	D	Br	$Pd(PPh_3)_4$	**6d**	64
5	MOM	A	Cl	$Pd(PPh_3)_4$	**6e**	<5
6	MOM	A	I	$Pd(PPh_3)_4$	**6e**	28
7	MOM	A	I	$Pd_2(dba)_3$, PPh_3	**6e**	69

[a] A: 2-methylsulfanylpyrimidin-4-yl; B: 4-methoxyphenyl; C: 4-nitrophenyl; D: pyrimidin-5-yl

mixture of tin derivatives **3a** and **4** in a ratio of 8 : 1.5, using integration of the *N*-Me ^{1}H-NMR signals at δ 3.51 for **3a** and at 3.49 for **4** to measure the proportion of the two compounds, spectroscopic data and thus evidence for the structure of **3a** were obtained from this mixture. Attempted separation by column chromatography using neutral alumina afforded only the minor product **4** together with **1b**, presumably *via* protonolysis of **3a**. The minor component, **4**, must arise from a competitive metallation at C-7 (see above[9]) (Scheme 2).



4 **2** R **5**
a Me
b MOM

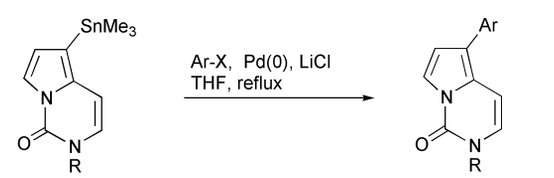
Scheme 2 *Reagents*: i: *n*-BuLi, THF, −90 °C, then Me_3SnCl, −90 °C to rt.

Similarly, **2b** gave a mixture of tin derivatives **3b** and **5** in a 8 : 1.5 ratio, measured by the integrated areas of methoxy ^{1}H-NMR signals – spectroscopic data and thus evidence for the structure of **3b** were obtained from this mixture. Application of column chromatography using neutral alumina afforded the minor tin derivative **5** and the pyrimidinone **1c**, from protonolysis of **3b** (Scheme 2). Lithiation of **2b** at C-3, leading to **5**, can be rationalized by MOM-assisted *ortho*-lithiation.

The location of the tin substituents in **4** and **5** was easily established by ^{1}H-NMR spectroscopy. The coupling system H6 H7 was absent in the spectrum of **4**, and only the higher field signal corresponding to H4 of the original H4 H5 pair remained in **5**.

Coupling reactions between **3a** and **3b** and several aryl and heteroaryl halides were conducted in THF at reflux using *ca.* 17 mol% of the catalyst, $Pd(PPh_3)_4$, or $Pd_2(dba)_3$ with PPh_3, and in the presence of LiCl in all cases (Scheme 3 and Table 1).

For most of the coupling reactions, the MOM protected tin derivative **3b** was chosen for the well known easy removal of the



3 R
a Me
b MOM

6 R Ar
a Me A
b MOM B
c MOM C
d MOM D
e MOM A

Scheme 3

protecting group[11] and also because it was obtained in a higher overall yield from the pyrrolopyrimidinone **1a**. The yield of coupled products from the bromobenzenes (entries 2 and 3) depended on the substituent. The withdrawing effect of the nitro substituent (and also of the π-deficient ring in 5-bromopyrimidine (entry 4)) had a positive effect and increased the yields in comparison with the bromo-benzene carrying a donor group (methoxy). Coupling of 4-halo-2-methylsulfanylpyrimidines with **3a** and **3b** (entries 1, 5, 6, and 7) was studied in more detail because of the closer analogy to the structure of variolin B. 4-Chloro-2-methylsulfanylpyrimidine was prepared as described[12] but gave a very low yield in a coupling reaction with **3b**. It was transformed[13] into 4-iodo-2-methylsulfanylpyrimidine and using $Pd(PPh_3)_4$, **3a** and the iodo-pyrimidine gave a moderate yield of **6a** (entry 1) but a low yield for reaction with **3b** to give **6e** (entry 6). The use of $Pd_2(dba)_3$, in conjunction with PPh_3, improved the yield of **6e** (entry 7) and thus permitted the preparation of a potential precursor for a synthesis of variolin B.

The ^{1}H-NMR spectrum of **6e** had lower field chemical shifts for H6 (δ 7.04 ppm) and especially H4 (δ 7.64 ppm) in comparison with the corresponding protons in **6d** (H6 at 6.87 and H4 at 6.66 ppm). These chemical shifts are due, probably, to the anisotropic effect of the pyrimidine N-2 lone pair on those hydrogens near in space.

All the tricyclic pyrimidinones were tested against murine lymphoma (P388D), human cell lung carcinoma (A549), human colon carcinoma (HT-29), and human melanoma (SK-MEL-28) cell lines but no significant activity was found at concentrations of 10 mg ml^{-1}.

Experimental

General

Melting points were determined in a capillary tube 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 Na_2SO_4, and solutions were evaporated under reduced pressure with a rotatory evaporator. IR spectra were performed on a Nicolet 205 FT-IR. NMR spectra were measured with Varian Gemini-200 (200 MHz), Varian Gemini-300 (300 MHz) and Varian VXR-500 (500 MHz) spectrometers; data are given in δ referenced to TMS. Mass spectra were measured in the electron impact (EI) mode with a Hewlett-Packard model 5989A. High resolution mass spectra were performed on a Autospec/VG by Departament de Química Orgánica Biològica (C.S.I.C.) Barcelona. Elemental analyses were performed on a C. E. Instruments EA-1108 in the Serveis Científico-Tècnics de la Universitat de Barcelona.

2-Methylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one 1b

A solution of **1a**[9] (480 mg, 3.6 mmol) in THF (25 ml) was added to a suspension of NaH (214 mg, 5.4 mmol) in THF

(3 ml) cooled at 0 °C. After the addition, the cooling bath was removed and when the reaction mixture reached rt, MeI (2.23 ml, 36 mmol) was added and the mixture was stirred for 15 h. After addition of CH_2Cl_2 (150 ml), the organic solution was washed with water, dried and evaporated to give a crude product which was purified by flash column chromatography. Elution with CH_2Cl_2 gave **1b** (490 mg, 93%) as a colourless oil, IR (film) ν/cm^{-1} 1688 (s, C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.53 (s, 3H, CH_3), 6.29 (dd, J = 3.5, 1.4 Hz, 1H, H5), 6.38 (d, J = 7.5 Hz, 1H, H4), 6.51 (d, J = 7.5 Hz, 1H, H3), 6.26 (dd, J = 3.5, 3.1 Hz, 1H, H6), 7.60 (dd, J = 3.1, 1.4 Hz, 1H, H7); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 36.2 (q, CH_3), 99.9 (d, C4), 103.7 (d, C5), 114.2 (d, C6), 114.3 (d, C7), 121.5 (d, C3), 130.7 (s, C4a), 145.9 (s, C1); found HRMS M$^+$ 148.0632, $C_8H_8N_2O$ requires M 148.0637.

2-Methoxymethylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one 1c

Following the same procedure used for **1b**, **1c** was prepared from **1a** (360 mg, 2.7 mmol), NaH (130 mg, 3.2 mmol) and MOMCl (224 µl, 3 mmol), after a reaction time of 30 min, the mixture was purified by flash column chromatography. Elution with CH_2Cl_2 gave **1c** (495 mg, 89%) as a colourless oil, IR (film) ν/cm^{-1} 1696 (s, C=O), 1634 (s, NCO), 1304 (m, C–O), 1095 (m); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.39 (s, 3H, CH_3), 5.28 (s, 2H, CH_2), 6.31 (dd, J = 3.4, 1.3 Hz, 1H, H5), 6.42 (d, J = 7.6 Hz, H4), 6.62 (dd, J = 3.4, 3.1 Hz, 1H, H6), 6.65 (d, J = 7.6 Hz, 1H, H3), 7.61 (dd, J = 3.1, 1.4 Hz, 1H, H7); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 56.5 (q, CH_3), 78.4 (t, CH_2), 100.6 (d, C4), 104.5 (d, C5), 114.6 (d, C6), 115.2 (d, C7), 123.0 (d, C3), 130.5 (s, C4a), 147.3 (s, C1); MS (EI) m/z 179 (11%), 178 (M$^+$, 100), 148 (91); found HRMS M$^+$ 178.0743, $C_9H_{10}N_2O_2$ requires M 178.0742.

2-Methylsulfonylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one 1d

To a solution of **1a** (560 mg, 4.2 mmol) and TEA (580 µl, 4.2 mmol) in CH_2Cl_2 (10 ml) at 0 °C, MsCl (380 µl, 4.2 mmol) was added. The reaction mixture was stirred for 30 min, and the temperature was allowed to rise to rt. The organic solution was washed with saturated aq NaCl, dried and evaporated. After purification by flash column chromatography, elution with CH_2Cl_2 gave **1d** (753 mg, 84%) as a white solid, mp 130–132 °C (hexane–CH_2Cl_2); IR (film) ν/cm^{-1} 1726 (s, C=O), 1356 (s, SO_2), 1171 (m), 1101 (m); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.62 (s, 3H, CH_3), 6.37 (dd, J = 3.5, 1.3 Hz, 1H, H5), 6.48 (d, J = 8.1 Hz, 1H, H4), 6.65 (dd, J = 3.5, 3.4 Hz, 1H, H6), 7.24 (d, J = 8.1 Hz, 1H, H3), 7.64 (dd, J = 3.4, 1.3 Hz, 1H, H7); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 42.1 (q, CH_3), 101.3 (d, C4), 106.9 (d, C5), 113.6 (d, C6), 116.4 (d, C7), 118.2 (d, C3), 129.5 (s, C4a), 145.2 (s, C1); MS (EI) m/z 213 (5%), 212 (M$^+$, 46), 134 (96), 133 (93), 105 (100); found HRMS M$^+$ 212.0251, $C_8H_8N_2O_3S$ requires M 212.0255.

2-(4-Methylphenylsulfonyl)pyrrolo[1,2-*c*]pyrimidin-1-(2*H*)-one 1e

Following the same procedure, from **1a** (300 mg, 2.2 mmol), TEA (6.2 ml, 44 mmol) and TsCl (640 mg, 3.4 mmol) in CH_2Cl_2 (10 ml), the reaction was conducted for 32 h at rt. Chromatographic purification, eluting with CH_2Cl_2 gave **1e** (500 mg, 78%) as a white solid. IR (film) ν/cm^{-1} 1720 (s, C=O), 1362 (s), 1303 (s, SO_2), 1175 (m), 1097 (m); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H, CH_3), 6.30 (dd, J = 3.5, 1.4 Hz, 1H, H5), 6.46 (d, J = 8.0 Hz, 1H, H4), 6.55 (dd, J = 3.5, 3.4 Hz, 1H, H6), 7.36 (d, J = 8.0 Hz, 2H, C3′, C5′), 7.47 (d, J = 8.0 Hz, 1H, H3), 7.49 (dd, J = 3.4, 1.4 Hz, 1H, H7), 8.0 (d, J = 8.0 Hz, 2H, C2′, C6′); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.7 (q, CH_3), 101.1 (d, C4), 106.4 (d, C5), 115.5 (d, C6), 116.2 (d, C7), 119.0 (d, C3), 127.0 (s, C4′), 127.8 (s, C1′), 129.3 (d, C3′, C5′), 129.6 (C2′, C6′), 133.9 (s, C4a), 146.0 (s, C1); MS (EI) m/z 288 (M$^+$, 31%), 133 (100); found HRMS M$^+$ 288.0569, $C_{14}H_{12}N_2O_3S$ requires M 288.0569.

General procedure for bromination of *N*-protected pyrrolo[1,2-*c*]-pyrimidin-1(2*H*)-ones 1b–e

To a solution of dihydropyrrolopyrimidinone **1b**–**e** in $CHCl_3$, NBS (1 equiv.) was added portionwise. The reaction mixture was stirred at rt until the total conversion of the starting material (TLC). The solution was washed four times with water, dried and evaporated to give the halogenated products **2a**–**c**.

5-Bromo-2-methylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one 2a. From NBS (589 mg, 3.3 mmol), **1b** (490 mg, 3.3 mmol) in CH_2Cl_2 (50 ml) then purification by flash column chromatography, eluting with hexane–CH_2Cl_2, **2a** (490 mg, 65%) was isolated as an oil, IR (film) ν/cm^{-1} 1695 (s, C=O), 710 (m, C–Br); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.53 (s, 3H, CH_3), 6.38 (d, J = 7.6 Hz, 1H, H4), 6.60 (d, J = 7.6 Hz, 1H, H3), 6.62 (d, J = 3.3 Hz, 1H, H6), 7.56 (d, J = 3.3 Hz, 1H, H7); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 36.5 (q, CH_3), 91.0 (s, C5), 98.1 (d, C4), 114.2 (d, C6), 116.5 (d, C7), 126.5 (d, C3), 128.8 (s, C4a), 144.6 (s, C1); MS (EI) m/z 229 (9%), 228 (^{81}BrM$^+$, 98), 227 (13), 226 (^{79}BrM$^+$, 100), 213 (18), 211 (18), 185 (36), 183 (38); found HRMS M$^+$ 225.9736, $C_8H_7{}^{79}BrN_2O$ requires M 225.9736.

5-Bromo-2-methoxymethylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one 2b. From **1c** (110 mg, 0.62 mmol) and NBS (110 mg, 0.62 mmol) in $CHCl_3$ (10 ml), reacting for 20 min, **2b** (140 mg, 90%) was obtained as a white solid requiring no further purification, IR (film) ν/cm^{-1} 1699 (s, CO), 1635 (s), 1317 (m, C–O), 1091 (m, C–O), 713 (s); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.39 (s, 3H, CH_3), 5.29 (s, 2H, CH_2), 6.45 (d, J = 7.7 Hz, 1H, H4), 6.64 (d, J = 3.3 Hz, 1H, H6), 6.75 (d, J = 7.7 Hz, 1H, H3), 7.57 (d, J = 3.3 Hz, 1H, H7); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 56.7 (q, CH_3), 78.6 (t, CH_2), 92.0 (s, C5), 98.9 (d, C4), 115.0 (d, C6), 116.9 (d, C7), 124.2 (d, C3), 128.5 (s, C4a), 146.6 (s, C1); MS (CI, CH_4) m/z 259 (16%), 258 (^{81}BrM$^+$, 26), 257 (22), 256 (^{79}BrM$^+$, 12), 227 (32), 225 (29); found HRMS M$^+$ 255.9846, $C_9H_9{}^{79}BrN_2O_2$ requires M 255.9847.

5-Bromo-2-methylsulfonylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one 2c. Following the general procedure, from **1d** (300 mg, 1.4 mmol) and NBS (252 mg, 1.4 mmol) in $CHCl_3$ (30 ml), reacting for 20 min and final purification by chromatography, eluting with CH_2Cl_2, gave **2c** (104 mg, 25%), IR (film) ν/cm^{-1} 1720 (s, C=O), 1350 (s, SO_2), 1173 (m); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.61 (s, 3H, CH_3), 6.49 (d, J = 8.0 Hz, 1H, H4), 6.67 (d, J = 3.4 Hz, 1H, H6), 7.32 (d, J = 8.0 Hz, 1H, H3), 7.60 (d, J = 3.4 Hz, 1H, H7); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 3.61 (s, 3H, CH_3), 94.5 (s, C5), 99.4 (d, C4), 116.1 (d, C6), 118.4 (d, C7), 119.4 (d, C3), 128.5 (s, C4a); MS (EI) m/z 293 (6%), 292 (^{81}BrM$^+$, 46), 291 (10), 290 (^{79}BrM$^+$, 43), 214 (91), 213 (100), 212 (91), 211 (96); found HRMS M$^+$ 289.9356, $C_8H_7{}^{79}BrN_2O_3S$ requires M 289.9347.

General procedure for preparation of *N*-protected 5-trimethylstannylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-ones, 3a–b

To a cooled (−90 °C) solution of the protected 5-bromodihydropyrrolopyrimidinone, **2a**–**b**, in THF was added quickly *n*-BuLi (1.6 M in pentane, 1.1 equiv.) and the reaction mixture was stirred for 5 min at the same temperature. After this time, Me_3SnCl (1 M in THF, 1.1 equiv.) was added and the reaction mixture was stirred for 1 h at −90 °C and then for 1 h at rt. The reaction mixture was diluted with ether and the organic layer washed with saturated aq NaCl. The organic solution was dried and evaporated.

2-Methyl-5-trimethylstannylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one 3a. From **2a** (60 mg, 0.26 mmol), *n*-BuLi (182 µl, 0.29 mmol) in THF (5 ml), **3a** (64 mg, 80%) was obtained as a colourless oil contaminated with **4** (15 mg, 15%), signals for **3a**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.30 (s, 9H, $Sn(CH_3)_3$), 3.51 (s,

3H, CH_3), 6.29 (d, J = 7.8 Hz, 1H, H4), 6.51 (d, J = 7.8 Hz, 1H, H3), 6.61 (d, J = 2.9 Hz, 1H, H6), 7.70 (d, J = 2.9 Hz, 1H, H7); found HRMS M^+ 312.0299, $C_{11}H_{16}N_2O^{120}Sn$ requires M 312.0284.

5-Bromo-2-methyl-7-trimethylstannylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one 4. Obtained as a by-product in preparation of **3a** by neutral alumina column chromatography, elution with hexane–CH_2Cl_2 gave **4**, while **3a** suffered protonolysis and consequently **1b** was recovered, ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0.31 (s, 9H, $Sn(CH_3)_3$), 3.49 (s, 3H, NCH_3), 6.39 (d, J = 7.6 Hz, 1H, H4), 6.56 (d, J = 7.6 Hz, 1H, H3), 6.68 (s, 1H, H6); MS (EI) m/z 375 (^{120}SnM–Me, 72%), 345 (52); found HRMS M^+ 389.9379, $C_{11}H_{15}{}^{79}BrN_2O^{120}Sn$ requires M 389.9389.

2-Methoxymethyl-5-trimethylstannylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one 3b. From **2b** (360 mg, 1.4 mmol), *n*-BuLi (960 µl, 1.5 mmol) in THF (10 ml), **3b** (403 mg, 85%) was obtained as a colourless oil contaminated with **5** (87 mg, 15%), data for **3b**: IR (film) ν/cm^{-1} 1697 (s, C=O), 1629 (m, C=C), 1300 (m, C–O), 1163 (m, C–O), 771 (m, C–Sn); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.33 (s, 9H, $Sn(CH_3)_3$), 3.39 (s, 3H, OCH_3), 5.30 (s, 2H, CH_2), 6.37 (d, J = 7.5 Hz, 1H, H4), 6.55 (d, J = 2.9 Hz, 1H, H6), 6.68 (d, J = 7.5 Hz, 1H, H3), 7.73 (d, J = 2.9 Hz, 1H, H7); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ −9.1 (q, $Sn(CH_3)_3$), 56.6 (q, NCH_3), 78.4 (t, CH_2), 78.6 (s, C5), 102.1 (d, C4), 116.2 (d, C6), 121.0 (d, C7), 123.1 (d, C3), 136.0 (s, C4a), 147.6 (s, C1); MS (EI) m/z 342 ($^{120}SnM^+$, 14%), 327 (100), 297 (30); $C_{12}H_{18}N_2O_2{}^{120}Sn$ requires M 342.

5-Bromo-2-methoxymethyl-3-trimethylstannylpyrrolo[1,2-*c*]-pyrimidin-1(2*H*)-one 5. Obtained as a by-product in the preparation of **3b** by neutral alumina column chromatography, elution with hexane–CH_2Cl_2 (1 : 1) gave **5** (15%) while **3b** suffered hydrolysis and consequently **1c** was recovered, ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 0.37 (s, 9H, $Sn(CH_3)_3$), 3.32 (s, 3H, OCH_3), 5.37 (s, 2H, CH_2), 6.49 (s, 1H, H4), 6.61 (d, J = 3.4 Hz, 1H, H6), 7.53 (d, J = 3.4 Hz, 1H, H7); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ −6.7 (q, $Sn(CH_3)_3$), 55.9 (q, OCH_3), 77.9 (t, CH_2), 108.0 (d, C4), 114.4 (d, C6), 116.7 (d, C7); MS (EI) m/z 420 ($^{120}Sn^{79}BrM^+$, 25%), 405 (44), 375 (100); found HRMS M^+ 419.9486, $C_{12}H_{17}{}^{79}BrN_2O_2{}^{120}Sn$ requires M 419.9495.

General procedure for coupling reactions of *N*-protected 5-trimethylstannylpyrrolopyrimidin-1(2*H*)-ones 3 with aryl or heteroaryl halides

A solution of *N*-protected 5-trimethylstannylpyrrolopyrimidinone, **3**, (1 equiv.), the aryl bromide (3 equiv.), LiCl (3 equiv.), and $Pd(PPh_3)_4$ (*ca.* 0.17 equiv.) in THF was refluxed for 24 h under argon. The reaction mixture was diluted with diethyl ether and the organic layer washed with saturated aq NaCl. The organic layer was dried and evaporated to give a crude material which was purified by flash column chromatography using mixtures of hexane and diethyl ether.

2-Methyl-5-(2-methylsulfanylpyrimidin-4-yl)pyrrolo[1,2-*c*]-pyrimidin-1(2*H*)-one 6a. Coupling involved **3a** (12 mg, 0.04 mmol), 4-chloro-2-methylsulfanylpyrimidine[11] (16 mg, 0.04 mmol), $Pd(PPh_3)_4$ (9 mg, 0.007 mmol) and LiCl (5 mg, 0.12 mmol) in THF (3 ml). Purification by chromatography, eluting with CH_2Cl_2 gave **6a** (4 mg, 40%), ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.63 (s, 3H, SCH_3), 3.60 (s, 3H, NCH_3), 6.78 (d, J = 7.6 Hz, 1H, H4), 7.02 (d, J = 3.4 Hz, 1H, H6), 7.12 (d, J = 5.3 Hz, 1H, H5′), 7.58 (d, J = 7.6 Hz, 1H, H3), 7.66 (d, J = 3.4 Hz, 1H, H7), 8.42 (d, J = 5.3 Hz, 1H, H6′); MS (EI) m/z 273 (18%), 272 (M^+, 100), 271 (22), 226 (30), 225 (41); found HRMS M^+ 272.0730, $C_{13}H_{12}N_4OS$ requires M 272.0731.

2-Methoxymethyl-5-(4-methoxyphenyl)pyrrolo[1,2-*c*]-pyrimidin-1(2*H*)-one 6b. Reaction involved **3b** (100 mg, 0.29 mmol), 1-bromo-4-methoxybenzene (110 µl, 0.87 mmol), $Pd(PPh_3)_4$ (68 mg, 0.05 mmol) and LiCl (37 mg, 0.88 mmol) in THF (4 ml). Final purification by chromatography, eluting with hexane–diethyl ether (7 : 3) gave **6b** (14 mg, 17%), ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.42 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.31 (s, 2H, CH_2), 6.42 (d, J = 6.6 Hz, 1H, H4), 6.65 (d, J = 6.6 Hz, 1H, H3), 6.77 (d, J = 3.3 Hz, 1H, H6), 6.98 (d, J = 8.5 Hz, 2H, H3′, H5′), 7.44 (d, J = 8.5 Hz, 2H, H2′, H6′), 7.66 (d, J = 3.3 Hz, 1H, H7); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 55.4 (q, CH_3), 56.7 (q, CH_3), 78.4 (t, CH_2), 100.1 (d, C4), 114.3 (d, C3′, C5′), 114.6 (d, C6), 115.3 (d, C7), 119.9 (s, C5), 123.4 (d, C3), 128.6 (d, C2′, C6′), 131.2 (s, C4a), 147.4 (s, C1), 158.3 (s, C4′); MS (EI) m/z 285 (19%), 284 (M^+, 100%), 254 (52), 239 (71); $C_{16}H_{16}N_2O_3$ requires M 284.

5-(4-Nitrophenyl)-2-methoxymethylpyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one 6c. From **3b** (100 mg, 0.29 mmol), 1-bromo-4-nitrobenzene (180 mg, 0.87 mmol), $Pd(PPh_3)_4$ (68 mg, 0.05 mmol) and LiCl (37 mg, 0.88 mmol) in THF (4 ml) and chromatographic purification eluting with hexane–CH_2Cl_2 (4 : 6) gave **6c** (55 mg, 63%) as a yellow solid, mp 162–163 °C (hexane–CH_2Cl_2); IR (KBr) ν/cm^{-1} 1711 (s, C=O), 1688 (m, C=C), 1596 (m, NO_2), 1344 (m, NO_2); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.43 (s, 3H, CH_3), 5.35 (s, 2H, CH_2), 6.74 (d, J = 7.7 Hz, 1H, H4), 6.86 (d, J = 7.7 Hz, 1H, H3), 6.89 (d, J = 3.3 Hz, 1H, H6), 7.66 (d, J = 8.9 Hz, 2H, H2′, H6′), 7.74 (d, J = 3.3 Hz, 1H, H7), 8.28 (d, J = 8.9 Hz, 2H, H3′, H5′); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 56.9 (q, CH_3), 78.6 (t, CH_2), 99.3 (d, C4), 114.3 (d, C6), 116.4 (d, C7), 117.9 (s, C5), 124.3 (d, C3′, C5′), 125.6 (d, C3), 127.5 (d, C2′, C6′), 128.1 (s, C4a), 141.8 (s, C1′), 145.8 (s, C4′), 147.0 (s, C1); MS (EI) m/z 300 (14%), 299 (M^+, 100), 269 (74); found HRMS M^+ 299.0903, C, 60.17; H, 4.37; N, 13.63%, $C_{15}H_{13}N_3O_4$ requires M 299.0906, C, 60.19; H, 4.39; N, 14.04%.

2-Methoxymethyl-5-(pyrimidin-5-yl)pyrrolo[1,2-*c*]pyrimidin-1(2*H*)-one 6d. From **3b** (100 mg, 0.29 mmol), 5-bromopyrimidine (140 mg, 0.88 mmol), $Pd(PPh_3)_4$ (68 mg, 0.05 mmol) and LiCl (37 mg, 0.88 mmol) in THF (4 ml), with purification by chromatography eluting with CH_2Cl_2–MeOH (97 : 3) gave **6d** (48 mg, 64%) as a white solid. Mp 143–144 °C (hexane–CH_2Cl_2); IR (KBr) ν/cm^{-1} 1688 (s, C=O), 1627 (m, C=C), 1460 (m), 1266 (m, C–O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.44 (s, 3H, CH_3), 5.35 (s, 2H, CH_2), 6.66 (d, J = 7.7 Hz, 1H, H4), 6.86 (d, J = 7.7 Hz, 1H, H3), 6.87 (d, J = 3.3 Hz, 1H, H6), 7.76 (d, J = 3.3 Hz, 1H, H7), 8.91 (s, 2H, H4′, H6′), 9.13 (s, 1H, H2′); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 56.9 (q, CH_3), 78.7 (t, CH_2), 98.7 (d, C4), 112.5 (s, C5), 113.7 (d, C6), 116.6 (d, C7), 125.6 (d, C3), 127.9 (s, C4a), 129.1 (s, C5′), 146.9 (s, C1), 154.7 (d, C4′, C6′), 156.3 (d, C2′); MS (EI) m/z 257 (16%), 256 (M^+, 100), 226 (98); found C, 60.96; H, 4.76; N, 21.77%, $C_{13}H_{12}N_4O_2$ requires C, 60.93; H, 4.72; N, 21.86%.

5-(2-Methylsulfanylpyrimidin-4-yl)-2-methoxymethylpyrrolo-[1,2-*c*]pyrimidin-1(2*H*)-one 6e. From **3b** (100 mg, 0.29 mmol), 4-iodo-2-methylsulfanylpyrimidine[12] (222 mg, 0.88 mmol), $Pd_2(dba)_3$·$CHCl_3$ (61 mg, 0.05 mmol), PPh_3 (46 mg, 0.18 mmol) and LiCl (37 mg, 0.88 mmol) in THF (4 ml), then purification by chromatography eluting with diethyl ether gave **6e** (72 mg, 69%) as a white solid, mp 125–126 °C (hexane–CH_2Cl_2); IR (KBr) ν/cm^{-1} 1693 (s, C=O), 1562 (m, C=N), 1360 (m, C–O), 1094 (m); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.65 (s, 3H, SCH_3), 3.44 (s, 3H, OCH_3), 5.37 (s, 2H, CH_2), 6.94 (d, J = 7.7 Hz, 1H, H3), 7.04 (d, J = 3.5 Hz, 1H, H6), 7.15 (d, J = 5.3 Hz, 1H, H5′), 7.64 (d, J = 7.7 Hz, 1H, H4), 7.69 (d, J = 3.5 Hz, 1H, H7), 8.46 (d, J = 5.3 Hz, 1H, H6′); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 14.3 (q, CH_3), 56.9 (q, CH_3), 78.8 (t, CH_2), 102.0 (d, C4), 111.8 (d, C5′), 113.3 (d, C6), 115.8 (s, C5), 116.3 (d, C7), 126.5 (d, C3), 130.6 (s, C4a), 131.8 (s, C4′), 146.9 (s, C1), 156.9 (d, C6′), 161.1 (s, C2′); MS (EI) m/z 303 (18%), 302 (M^+, 100), 272 (M − 30, 28); found HRMS M^+ 302.0831, $C_{14}H_{14}N_4O_2S$ requires M 302.0837.

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