Enforced Helicity: Efficient Access to Self-Organized Helical Molecular Strands by the Imine Route

Kevin M. Gardinier, Richard G. Khoury, and Jean-Marie Lehn*[a]

Abstract: The condensation of the two oligoheterocyclic aldehydes **8** and **16** with the bis-hydrazine **17** gives the bis-hydrazones **1** and **2**. These molecular strands are shown to adopt helical conformations of 1.5 and 2.5 turns, respectively. The helical shape of **1** has been confirmed and structurally characterized by X-ray crystallography. The results indicate that the pyrimidine-hydrazone unit is a satisfatory helicity codon, so that the facile hydrazone formation provides an efficient procedure for generating helical structures. This greatly widens the scope of the methodology based on designed heterocyclic sequences for enforcing helicity in molecular strands, and opens interesting routes towards a variety of derived structures.

Keywords: helical structures · heterocycles · hydrazones · pyrimidine · self-organization

Introduction

Intramolecular self-organization processes lead to the generation of specific molecular architectures on the basis of the nonbonded interactions and conformational features present in the molecular structures. To gain control over such events by adequate design requires the identification of structural elements that encode specific organizational information and their incorporation into the molecular entity. As a result, it should become possible to enforce the spontaneous but controlled generation of well-defined architectures. Thus, molecular strands may be induced to fold in particular into helical or bent shapes, as is the case for biological entities such as the α-helices and β-turns of proteins[1] and the double helix of nucleic acids. Increased activity has recently been devoted to such intramolecular self-organization events in order to establish control over synthetic systems, to gain understanding of the folding patterns of biomolecules,[2] and to generate defined chemical-biological hybrid structures. In particular, the goal of gaining a better understanding of the factors controlling helix formation in biopolymers has prompted active research towards the synthesis of non-natural helical systems.[3, 4] Helical self-organization has thus been demonstrated in organic systems composed of various units, such as unnatural amino acids[5] and oligo-aromatic groups.[6] Other helical systems have been designed which utilize non-covalent interactions such as hydrogen bonding or metal-ligand coordination.[3, 4, 7, 8]

We have recently reported the enforced generation of helices based on *"helicity codons"* that involve pyrimidine-pyridine[9a–e] or pyridine-pyridazine[9f] sequences which display a *transoid* geometry about the single bonds between all adjacent heterocycles. Although helical structures with up to four turns have been obtained,[9e] the synthesis of such long strands is very challenging, and other procedures were sought that may provide a more direct access to these systems. As a continuation of our investigations into helical molecular self-organization, we wish to present here our work toward the generation of extended helical entities on the basis of functionalized helical motifs which may be connected through facile imine bond formation.

Basic design: Imine condensation was envisioned to be a useful method for extending helical architectures. The condensation of an aryl aldehyde and a benzylic amine should provide preferentially a *trans*-imine group in which the X–N=CH geometry would closely mimic the corresponding fragment of the pyridine subunit used in the previously described helices.[9] In addition, if α-substituted *N*-heterocyclic derivatives are used, the system may be expected to adopt a *transoid-transoid* conformation between pyrimidine-imine-pyrimidine nitrogens, since this conformation minimizes all secondary steric and electronic interactions (Scheme 1). Though this conformation is flexible and others can exist for this imine unit, molecular selection for the proposed conformer is expected to be more favored as the helical units become longer due to increased stacking between turns. Other imine geometries should be less favorable since the

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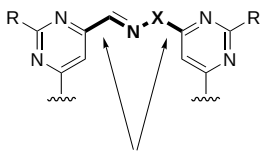


Scheme 1. The *transoid-transoid* imine/hydrazone conformation satisfies the steric and electronic factors that govern conformational selection and presents a geometry isosteric with the corresponding fragment in a pyridine group.

helical units would be farther apart and, therefore, could not stack in a cooperative manner. In addition, a hydrazone unit (X = NH, Scheme 1) was expected to add conformational rigidity and planarity, through cross-conjugation, relative to a methylene group (X = CH_2).

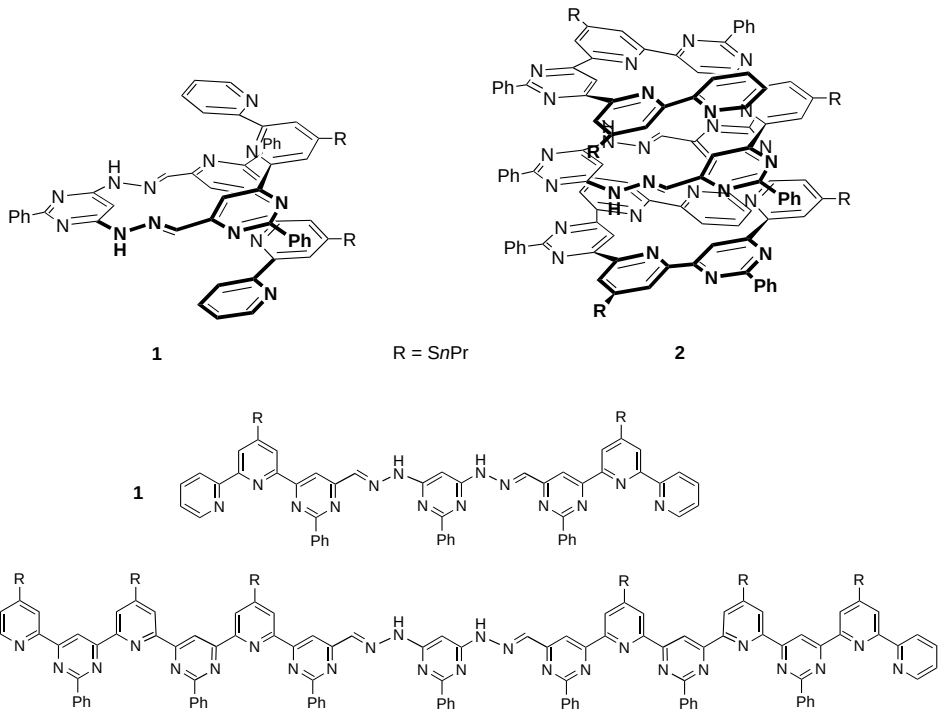
Based on these premises, we report here the generation of the helical entities **1** and **2**, which possess a bis-hydrazone spacer unit that adopts the *transoid-transoid* conformation along both hydrazone functionalities (Scheme 2). The phenyl substituents of the pyrimidine groups were envisioned to increase the stability of the helix through additional stacking interactions and to render the pyrimidine units less sensitive to reaction conditions. The synthesis is based on the condensation of the required aldehyde components **8** and **15** with the dihydrazinopyrimidine spacer unit **17** (Schemes 3, 4, and 5 below).

Abstract in French: *La condensation des deux aldéhydes oligohétérocycliques **8** et **16** avec la bishydrazine **17** fournit les bishydrazones **1** et **2**. Ces brins moléculaires adoptent une conformation hélicoïdale comportant respectivement 1,5 et 2,5 tours. La forme hélicoïdale de **1** a été confirmée et sa structure caractérisée par radio cristallographie. Ces résultats indiquent que l'unité (pyrimidine-hydrazone) est un condon d'hélicité satisfaisant, ouvrant ainsi une voie d'accès efficace à la génération de structures hélicoïdales par formation d'hydrazone. Il en résulte une extension notable de la portée de la méthodologie mettant en oeuvre des séquences hétérocycliques spécifiques pour imposer une hélicité à des brins moléculaires. D'intéressantes perspectives sont ainsi ouvertes vers une variété de nouvelles structures.*

Results and Discussion

Synthesis of strands 1 and 2: The synthesis of aldehyde **8** is outlined in Scheme 3. Condensation of benzamidine hydrochloride with β-keto ester **3** gave a pyrimidone, which was treated with trichlorophosphoric acid to yield the chloropyrimidine **4**. Stille coupling of **4** with tributyl(1-ethoxyvinyl)-stannane[10] followed by hydrolysis gave ketone **5**. Consistent with our previous work in this area,[9] we chose the Potts method for the synthesis of the present pyrimidine-pyridine compounds.[11] Michael addition of **5** to the pyridine Michael acceptor **6** followed by treatment with ammonium acetate gave **7**. Lewis acid mediated deprotection of the methyl ether with BBr_3 gave the corresponding alcohol that was oxidized under Swern conditions to give aldehyde **8**.

The longer aldehyde **15** was prepared as shown in Scheme 4. In a convergent approach toward **15**, both required subunits were obtained from 2-phenyl-4,6-dichloropyrimidine (**9**). On one hand, compound **9** was desymmetrized by a statistical Stille coupling with tributyl(1-ethoxyvinyl)stannane. The pyrimidine monovinyl ether was hydrolysed, and the resulting ketone was subjected to an additional Stille cross-coupling to give **10**. Potts condensation of **10** with **6**,[11]



Scheme 2. Representation of compounds **1** and **2** in their optimal helical form (top), as well as in their extended form for clarity (bottom). The helical structures **1** and **2** display a *transoid-transoid* conformation across both hydrazone units; this allows for efficient stacking interaction between the aromatic motifs.

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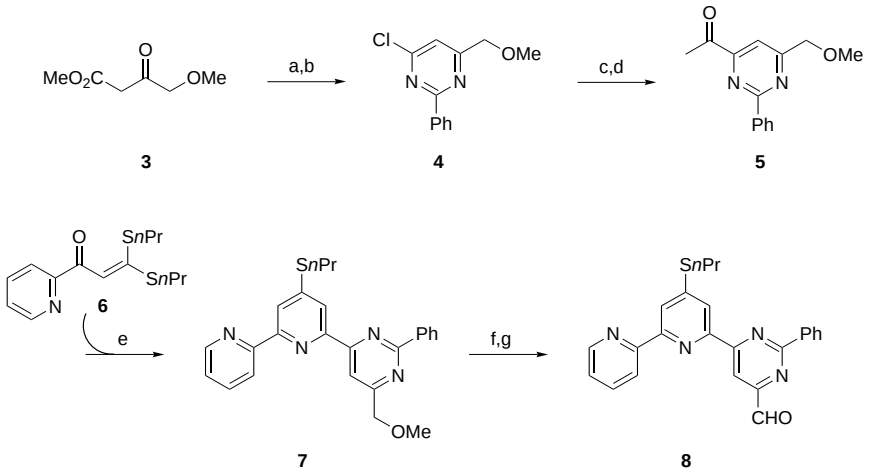


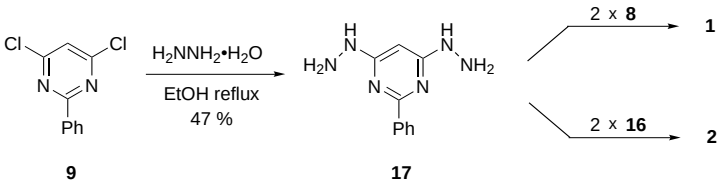
Scheme 3. a) $PhC(NH)NH_2 \cdot HCl$, NaOMe, EtOH; b) $POCl_3$, 57%, 2 steps; c) $Bu_3SnC(CH_2)OEt$, $[Pd(PPh_3)_2Cl_2]$, DMF; d) 2N HCl, acetone, (93%, 2 steps); e) NaH, THF, then NH_4OAc, AcOH, (60%); f) BBr_3, CH_2Cl_2; g) DMSO, $(COCl)_2$, CH_2Cl_2, (80%, 2 steps).

The helicity of both **15** and **16** is indicated by the proton NMR spectra. Since the terminal pyridine group lies above the plane of the terminal pyrimidine, an anisotropic upfield shift of the terminal pyridine proton resonances is observed (H2 and H3 at $\delta =$ 6.71). This is consistent with the shifts observed in the previously described helices.[9] Dichloropyrimidine **9** was also used in the preparation of the dihydrazinopyrimidine **17**. Addition of two equivalents of hydrazine to **9** was achieved in refluxing ethanol to give the desired spacer component.

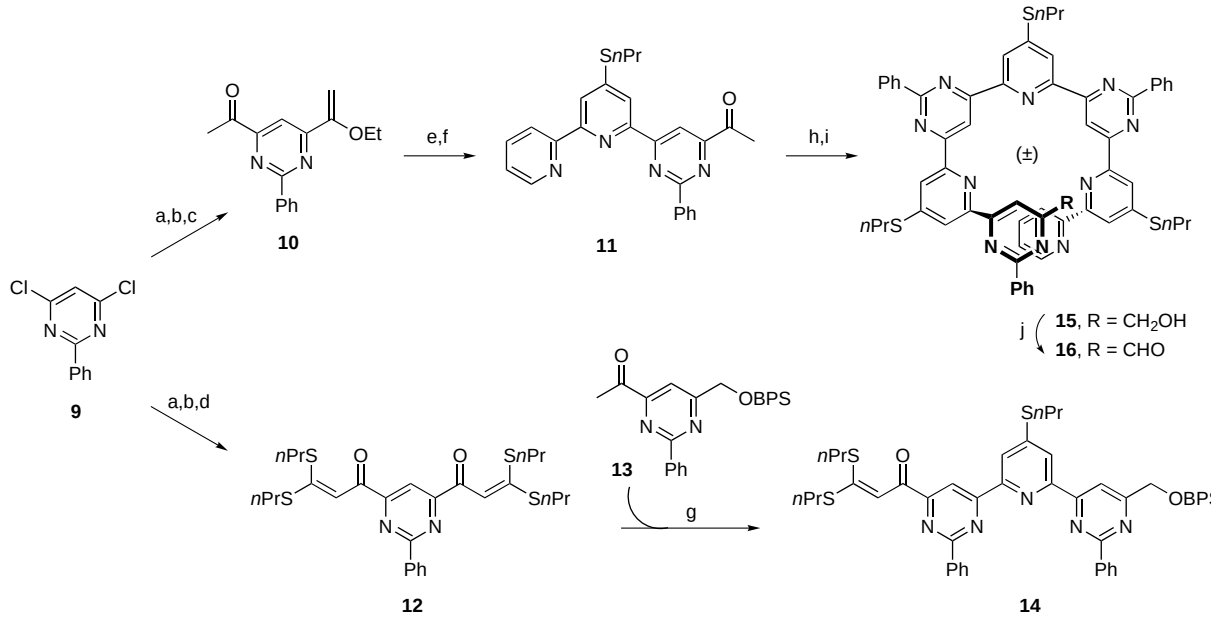
Finally, the strands **1** and **2** were obtained by the condensation of **17** with two equivalents of the aldehydes **8** and **16**, respectively (Scheme 5).

followed by hydrolysis of the remaining vinyl ether to led the subunit **11** in 27% overall yield from **9**.

On the other hand, double Stille coupling of **9** with the tributyl(1-ethoxyvinyl)stannane, followed by hydrolysis and successive treatment with sodium hydride, carbon disulfide, and propyl iodide yielded the Michael acceptor **12**. Potts coupling of **12** with one equivalent of **13** gave the second subunit **14** in 54% overall yield from **9**. Ketone **13**, rather than ketone **5**, was used as the coupling partner with **12**, since removal of the methyl ether at a later stage proved difficult. Potts coupling of **14** with **11** and removal of the silyl protecting group gave the alcohol **15**. Finally, oxidation of **15** under Swern conditions led to the aldehyde **16** in 56% yield from **13**.



Scheme 5. Synthesis of the dihydrazinopyrimidine **17** and of compounds **1** and **2**.



Scheme 4. a) $Bu_3SnC(CH_2)OEt$ [for **9**, 1 equiv; for **10**, 2 equiv], 3 mol% $[Pd(PPh_3)_2Cl_2]$, DMF, 80°C; b) 2N HCl, acetone, RT; c) $Bu_3SnC(CH_2)OEt$, 5 mol% $[Pd(PPh_3)_2Cl_2]$, DMF, 80°C (47%, 3 steps); d) NaH, CS_2, PrI, DMSO, RT (88%, 3 steps); e) **6**, KO*t*Bu, THF, RT, then NH_4OAc, AcOH, 80°C; f) 2N HCl, acetone, RT (58%, 2 steps); g) KO*t*Bu, THF, 45°C, then NH_4OAc, AcOH, 80°C (61%); h) NaH, THF 45°C, then NH_4OAc, AcOH, 80°C; i) Bu_4NF, THF, RT; j) DMSO, $(COCl)_2$, CH_2Cl_2, −78°C (56%, 3 steps).

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Helical conformation of the bis-imino strands 1 and 2

^1H NMR spectroscopy: As demonstrated in earlier work,[9] the formation of a helical structure in polyheterocyclic strands is revealed by characteristic upfield shifts in the proton NMR spectra. Thus, the presence of terminal pyridine proton signals at $\delta = 6.71$ for H2 and H3 indicates that both **15** and **16** adopt a helical conformation.

The bis-imino strands **1** and **2** displayed ^{1}H NMR features diagnostic of helix formation. As expected the proton spectrum of **1** shows an upfield shift of the terminal pyridine hydrogens H2 and H3 at $\delta = 7.02$ and 6.48, respectively.[12] Compound **2**, prepared from an already helically organized aldehyde, shows an increase in the anisotropic shift of the terminal pyridine protons H2 and H3 (not shown) to $\delta = 6.44$ and 6.30, respectively, as compared with the starting aldehyde **15** (both at $\delta = 6.71$ ppm). This increase is consistent with a cumulative effect of the two helical motifs resulting from increased stacking within the system. A similar progressive increase in the anisotropic effect on pyridine H2 and H3 proton signals has been observed in previously described pyridine-pyrimidine helices ranging from 1 to 4 turns.[9c,d,e]

On the basis of these NMR data, one may conclude that the molecular strands **1** and **2** as well as **15** (and **16**) adopt a helical conformation of about 1.5, 2.5, and 1 turns respectively.

*Crystal structure of compound **1***: The helical shape of the bis-imino strand **1** was confirmed and characterized by X-ray crystallography. The crystal structure, shown in Figure 1, has a centrosymmetric cell that contains eight molecules of **1** (four enantiomeric pairs) and one molecule of tetrahydrofuran. Compound **1** displays a helical shape with overlap between the three terminal rings; this defines a cavity of 5.05 Å diameter. The distance between the plane containing the hydrazone and the pyrimidine group and the plane containing the two terminal pyridine groups is 3.44 Å, that is, it corresponds to a van der Waals contact. With respect to the plane defined by the hydrazone subunit, the torsional angles between the hydrazone and external pyrimidine groups are between 18.0° and 19.0°; these values are considerably larger than the 9° – 14° angles present within the pyridine-pyrimidine based helices previously reported by our group.[9c,d,e] On the other hand, the torsional angles between the hydrazone unit and the central pyrimidine group lie between 6.0° and 8.4° and are consistent with those found in the pyridine-pyrimidine based helices. Finally the structure possesses a helical pitch of 3.46 Å.

Conclusion

The present results show that imine condensation is a simple and efficient method for extending helical architectures in polyheterocyclic molecular strands. The dihydrazone unit adopts a *transoid-transoid* conformation about both hydrazone functionalities in compounds **1** and **2** and allows for a

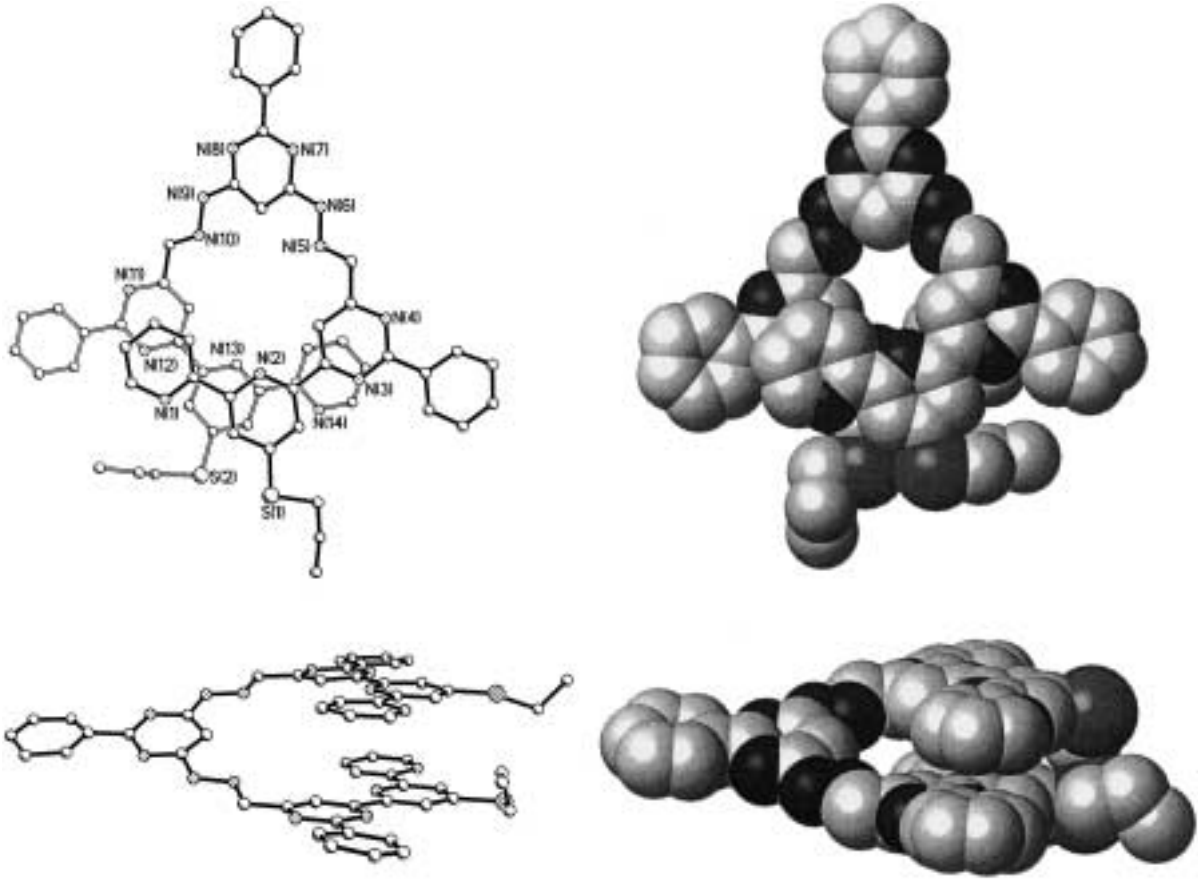

Figure 1. Crystal structure of helix **1**; view perpendicular to (top) and along (bottom) the helical axis, in ball-and-stick (left) and space filling (right) representations. The hydrogen atoms are omitted for clarity.

pronounced overlap between the helical motifs. Crystallographic analysis of **1** confirms that it possesses a well-defined helical structure and that the hydrazone functionality is a good substitute for a pyridine group. The proton NMR data unambiguously indicate that strand **2** adopts, in solution, an extended helical structure, which may be estimated to possess about 2.5 turns. It therefore appears that the pyrimidine-hydrazone unit is a satisfactory *helicity codon*, with features comparable to the previously used pyrimidine-pyridine group.[9c,d,e] This property may be expected to greatly increase the scope of the methodology to enforce helical architectures into molecular strands. In particular, this facile method for lengthening helical motifs through hydrazone formation may provide an efficient entry into a new class of helical polymers that possess interesting physical and mechanical properties.

Experimental Section

General: All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. The following solvents were distilled immediately prior to use: tetrahydrofuran (THF) and diethyl ether from sodium and benzophenone, and dichloromethane (CH_2Cl_2) from calcium hydride under Ar. *N*,*N*-Dimethylformamide (DMF) was obtained from a Sure-Seal™ bottle and used as received. Triethylamine was distilled from potassium hydroxide. All organic solutions were routinely dried by using magnesium sulfate ($MgSO_4$) or sodium sulfate (Na_2SO_4), and solvents were removed under vacuum using a rotary evaporator. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC200 spectrometer at 200 MHz and 50 MHz, respectively. Spectra were obtained by using $CDCl_3$, unless otherwise noted, with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (δ) and coupling constants (J) are reported in Hertz. Flash chromatography, according to the method of Still,[13] was performed by using 230–400 mesh silica gel particles or on neutral alumina (activity 2) supplied by Merck. Microanalyses were performed by the Service Central de Microanalyse du CNRS, Faculté de Chimie, Strasbourg. Melting points were measured on a digital electrothermal apparatus and are uncorrected.

4-Chloro-6-methoxymethyl-2-phenylpyrimidine (4): A solution of sodium methoxide in methanol (113 mL, 708 mmol) was added dropwise through addition funnel to a solution of benzamidine hydrochloride (36.55 g, 233.4 mmol) and methyl 4-methoxyacetoacetate (29.0 mL, 217.3 mmol) in anhydrous ethanol (180 mL). After addition, the mixture was heated to reflux for 21 h under an N_2 atmosphere. Thereafter it was concentrated in vacuo and dried under high vacuum for 3 hours. The white solid was dissolved in water (800 mL) and acidified to pH 3 with concentrated HCl. The white precipitate was collected by filtration, washed with water until the eluant was pH 7, and then dried under high vacuum overnight. The white solid (44.0 g) was subjected to the next reaction without further purification. $POCl_3$ (200 mL) was slowly added to a 1 L flask that contained the above white solid. The mixture was heated to reflux for 3 h (dissolution occurs between 30–40 °C). The excess $POCl_3$ was removed in vacuo, and the resulting paste was cooled to 0 °C and carefully treated with ice water (400 mL). The mixture was extracted with EtOAc (3×200 mL). The combined organic layers were washed with H_2O (2×150 mL), saturated $NaHCO_3$ (200 mL), and brine (200 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by flash chromatography (SiO_2, 10% diethyl ether/hexanes) to give **4** (29.0 g, 57% for 2 steps) as a white solid. M.p. 42 °C; ^{1}H NMR: $\delta = 3.53$ (s, 3H), 4.60 (s, 2H), 7.38 (s, 1H), 7.48 (m, 3H), 8.42 (m, 2H); ^{13}C NMR: $\delta = 59.1$, 74.0, 115.7, 128.5, 128.6, 131.3, 136.1, 162.2, 164.8; elemental analysis calcd (%) for $C_{12}H_{11}N_2OCl$ (234.69): C 61.42, H 4.72, N 11.94; found C 61.45, H 4.67, N 12.34.

1-(6-Methoxymethyl-2-phenylpyrimidin-4-yl)ethanone (5): Tributyl(1-ethoxyvinyl)stannane (17.64 g, 48.84 mmol) and *trans*-bis(triphenylphosphine)palladium dichloride (799 mg, 1.14 mmol) were added to a solution of **4** (9.93 g, 42.2 mmol) in DMF (50.0 mL). The solution was stirred at 80 °C for 24 h under N_2 atmosphere. Diethyl ether (100 mL) and an aqueous solution of KF (6.57 g in 50 mL H_2O) were added and the mixture was stirred vigorously for 40 min at RT. The mixture was filtered, and the solid was washed with additional diethyl ether (150 mL). The organic phase from the filtrate was washed with H_2O (100 mL) and brine (100 mL), dried, filtered, and concentrated. The crude material was dissolved in acetone (75 mL) and HCl (2 N, 30 mL) and stirred overnight at RT. The mixture was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3×75 mL). The combined organic layers were washed with saturated $NaHCO_3$ (75 mL), dried over $MgSO_4$, filtered, and concentrated. Recrystallization from hexanes gave **5** (9.47 g, 93%) as white needles. M.p. 92 °C; ^{1}H NMR: $\delta =$ 2.82 (s, 3H), 3.54 (s, 3H), 4.68 (d, $J = 0.6$ Hz, 3H), 7.52 (m, 3H), 7.91 (s, 1H), 8.52 (m, 2H); ^{13}C NMR: $\delta = 25.5$, 59.0, 74.3, 111.2, 128.2, 131.0, 136.7, 159.5, 164.0, 170.2, 199.8; elemental analysis calcd (%) for $C_{14}H_{14}N_2O_2$ (242.28): C 69.41, H 5.82, N 11.56; found C 69.51, H 5.62, N 11.79.

6-(6-Methoxymethyl-2-phenylpyrimidin-4-yl)-4-propylsulfanyl[2,2′]bipyridinyl (7): NaH (38 mg, 0.95 mmol; 60% dispersion in mineral oil) was added to a solution of **5** (202 mg, 0.834 mmol) in THF (5.0 mL) at 0 °C. The mixture was stirred at RT for 30 min then a solution of **6** (191 mg, 0.874 mmol) in THF (2.0 mL; 3×0.5 mL rinse) was added by cannula. The solution was stirred at 35 °C for 20 h under N_2 atmosphere. Ammonium acetate (1.0 g) and glacial acetic acid (4.0 mL) were added, and the mixture was stirred at 80 °C for 1h. The dark red solution was cooled to RT, poured into H_2O (20 mL), and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (30% EtOAc/hexane) and recrystallized from hexane to give **7** (214 mg, 60%) as a white solid. M.p. 122 °C; ^{1}H NMR: $\delta = 1.16$ (t, $J = 7.3$ Hz, 3H), 1.88 (sext, $J = 7.3$ Hz, 2H), 3.20 (t, $J = 7.6$ Hz, 2H), 3.61 (s, 3H), 4.74 (s, 2H), 7.35 (m, 1H), 7.54 (m, 3H), 7.89 (dt, $J = 1.8$, 7.9 Hz, 1H), 8.44 (d, $J = 1.8$ Hz, 1H), 8.52 (s, 1H), 8.58–8.72 (m, 5H); ^{13}C NMR: $\delta = 13.5$, 22.0, 32.8, 59.1, 74.9, 112.0, 118.6, 118.9, 121.4, 123.9, 128.3, 128.4, 130.6, 136.8, 137.6, 149.0, 151.9, 153.2, 155.2, 155.5, 163.2, 163.6, 168.7; elemental analysis calcd (%) for $C_{25}H_{24}N_4OS$ (428.55): C 70.07, H 5.64, N 13.07; found C 70.09, H 5.72, N 12.92.

2-Phenyl-6-(4-propylsulfanyl-[2,2′]bipyridinyl-6-yl)-pyrimidine-4-carbaldehyde (8): A solution of BBr_3 (1 M, 7.7 mL, in CH_2Cl_2) was added by syringe to a solution of **7** (833 mg, 1.94 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The solution was stirred at 0 °C for 15 min, then at RT for 1.5 h. The solution was again cooled to 0 °C and quenched by slow addition of diethyl ether (20 mL), H_2O (20 mL), and NaOH (1 N, 25 mL). The mixture was stirred at RT for 1 h and then extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with H_2O (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (80% EtOAc/hexanes) to give 4-hydroxymethyl-2-phenyl-6-(4-propylsulfanyl-[2,2′]bipyridinyl-6-yl)-pyrimidine (**7a**) (730 mg, 91%) as a white solid. M.p. 125 °C. ^{1}H NMR: $\delta = 1.13$ (t, $J = 7.3$ Hz, 3H), 1.84 (sext, $J = 7.3$ Hz, 2H), 3.13 (t, $J = 7.6$ Hz, 2H), 4.00 (s, 1H), 4.90 (s, 2H), 7.51 (m, 3H), 7.82 (dt, $J = 1.8$, 7.9 Hz, 1H), 8.26 (s, 1H), 8.34 (d, $J = 1.8$ Hz, 1H), 8.47 (d, $J = 1.8$ Hz, 1H), 8.48 (m, 1H), 8.55 (m, 2H), 8.68 (m, 1H); ^{13}C NMR: $\delta = 13.5$, 22.0, 32.8, 63.9, 111.4, 118.6, 118.9, 121.4, 124.0, 128.2, 128.5, 130.9, 136.9, 137.2, 149.0, 152.1, 152.7, 155.2, 155.4, 162.7, 163.3, 168.9; elemental analysis calcd (%) for $C_{24}H_{22}N_4OS$ (414.52): C, 69.54, H 5.35, N 13.52; found C 69.41, H 5.21, N 13.37.

DMSO (0.180 mL, 2.54 mmol) was added to a solution of oxalyl chloride (0.110 mL, 1.26 mmol) in CH_2Cl_2 (2.0 mL) at −78 °C. The solution was stirred at −78 °C for 10 min, and then a solution of alcohol **7a** (212 mg, 0.511 mmol) in CH_2Cl_2 (2.50 mL) was added by cannula. The solution was stirred at −78 °C for 30 min then at −45 °C for 30 min. Triethylamine (1.60 mL) was added, and the mixture was warmed to RT and poured into saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The solid was washed with acetone to provide **8** (184 mg, 87%) as a light yellow solid. M.p. 168 °C. ^{1}H NMR: $\delta =$ 1.16 (t, $J = 7.3$ Hz, 3H), 1.88 (sext, $J = 7.3$ Hz, 2H), 3.20 (t, $J = 7.3$ Hz, 2H), 7.37 (m, 1H), 7.58 (m, 3H), 7.90 (dt, $J = 1.8$, 7.6 Hz, 1H), 8.46 (d, $J = 1.8$ Hz, 1H), 8.56 (d, $J = 1.8$ Hz, 1H), 8.66 (m, 3H), 8.70 (s, 1H), 10.13 (s, 1H); ^{13}C NMR: $\delta = 13.5$, 22.0, 32.8, 111.0, 118.5, 119.2, 121.5, 124.1, 128.4, 128.6, 131.3, 136.6, 149.0, 152.2, 152.2, 155.1, 155.4, 159.3, 165.1, 193.4; elemental analysis calcd (%) for $C_{24}H_{20}N_4OS$ (412.51): C 69.88, H 4.89, N 13.58; found C 69.73, H 4.76, N 13.40.

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4,6-Dihydrazino-2-phenylpyrimidine (17): Hydrazine hydrate (10.0 mL) was added to a solution of **9**[9b] (2.50 g, 11.1 mmol) in absolute ethanol (75.0 mL). The solution was heated to reflux for 3 d. The reaction was concentrated, the excess hydrazine hydrate was decanted, and the remaining orange solid was triturated with water then recrystallized from methanol to give **17** (1.12 g, 47%) as a white solid. M.p. 142 °C; ^{1}H NMR: $\delta = 3.70$, (br s, 4H), 5.81 (s, 1H), 6.74 (br s, 2H), 7.41 (m, 3H), 8.26 (m, 2H). FAB-MS: *m/z*: 216.2 ($C_{10}H_{12}N_6$ requires 216.112); ^{13}C NMR: $\delta = 78.0$, 127.9, 128.2, 130.0, 138.3, 163.3, 166.6; elemental analysis calcd (%) for $C_{10}H_{12}N_6$ (216.25): C 55.54, H 5.59, N 38.86; found C 56.10, H 5.50, N 39.09.

4,6-Bis-{*N*′-[2-phenyl-6-(4-propylsulfanyl[2,2′]bipyridinyl-6-yl)-pyrimidin-4-ylmethylene]hydrazino}-2-phenylpyrimidine (1): A solution of aldehyde **8** (39.9 mg, 0.0967 mmol) and **17** (10.6 mg, 0.049 mmol) in $CDCl_3$ (0.5 mL) was warmed to 55 °C overnight. The mixture was concentrated and the crude material was purified by flash chromatography (alumina, 30% EtOAc/ hexanes) to give **1** (44 mg, 89%) as a white powder. M.p. 236.5 °C; ^{1}H NMR: $\delta = 1.21$ (t, $J = 7.3$ Hz, 6H), 1.91 (sext, $J = 7.6$ Hz, 4H), 3.17 (t, $J = 7.6$ Hz, 2H), 6.49 (m, 2H), 7.06 (dt, $J = 1.5$, 7.6 Hz, 2H), 7.55 (m, 10H), 7.75 (s, 2H), 7.94 (d, $J = 1.5$ Hz, 2H), 8.08 (d, $J = 1.8$ Hz, 2H), 8.21 (m, 4H), 8.50 (m, 6H), 8.66 (s, 2H), 9.78 (br s, 2H); ^{13}C NMR: $\delta = 13.7$, 22.0, 32.8, 83.4, 110.3, 118.0, 120.5, 122.8, 128.1, 128.4, 128.9, 130.6, 130.8, 135.7, 137.6, 140.8, 148.1, 151.0, 151.6, 153.8, 154.4, 161.0, 162.2, 162.7, 163.3, 164.4; FAB-MS: *m/z* (%): 1005.2 (100) $[M+H]^+$; HRMS (FAB-MS): calcd for $C_{58}H_{48}S_2N_{14}$ 1005.3706; found 1005.3705; elemental analysis calcd (%) for $C_{58}H_{48}S_2N_{14} \cdot 2H_2O$ (1041.26): C 66.91, H 5.03, N 18.83; found C 66.79, H 4.89, N 17.95.

1-[6-(1-Ethoxyvinyl)-2-phenylpyrimidin-4-yl]ethanone (10): Compound **9** (5.92 g, 26.3 mmol) and $[Pd(PPh_3)_2Cl_2]$ (524 mg, 0.746 mmol) were added to a solution of tributyl(1-ethoxyvinyl)stannane (9.65 g, 26.7 mmol) in DMF (27 mL). The solution was stirred at 80 °C for 20 h under N_2 atmosphere. The solution was cooled to 0 °C, and quenched with diethyl ether (27 mL) and an aqueous solution of KF (2.8 g in 27 mL H_2O). After stirring for 1 h, the mixture was filtered, and the solid was washed well with additional diethyl ether (100 mL). The filtrate was washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude vinyl ether was purified by flash chromatography, then dissolved in acetone (30 mL) and HCl (2 N, 13 mL). The solution was stirred at RT for 16 h, then at reflux for 1 h. The solution was cooled to RT, poured into H_2O (50 mL), and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (5–10% diethyl ether/hexanes) to give 4-acetyl-6-chloro-2-phenylpyrimidine (**9a**; 3.43 g, 56%) which was used directly in the next reaction. M.p. 74 °C. ^{1}H NMR: $\delta = 2.80$ (s, 3H), 7.52 (m, 3H), 7.74 (s, 1H), 8.49 (m, 2H); ^{13}C NMR: $\delta = 25.8$, 115.4, 128.6, 128.7, 132.0, 135.4, 160.4, 163.4, 165.6, 198.4.

Compound **9a** (3.39 g, 14.6 mmol) and $[Pd(PPh_3)_2Cl_2]$ (337 mg, 0.480 mmol) were added to a solution of tributyl(1-ethoxyvinyl)stannane (6.17 g, 17.1 mmol) in DMF (20 mL). The solution was stirred at 80 °C for 16 h under N_2 atmosphere. The solution was cooled to 0 °C, and then quenched with diethyl ether (25 mL) and a solution of KF (1.8 g) in H_2O (20 mL). After stirring for 1 h, the mixture was filtered, and the solid was washed with additional diethyl ether (125 mL). The filtrate was washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by flash chromatography (10% diethyl ether/hexanes) to give **10** (3.29 g, 84%) as a white solid. M.p. 90 °C; ^{1}H NMR: $\delta = 1.48$ (t, $J = 7.0$ Hz, 3H), 2.83 (s, 3H), 4.01 (quart, $J = 7.0$ Hz, 2H), 4.58 (d, $J = 1.8$ Hz, 1H), 5.90 (d, $J = 2.1$ Hz, 2H), 7.52 (m, 3H), 8.06 (s, 1H), 8.57 (m, 2H); ^{13}C NMR: $\delta = 14.4$, 25.7, 63.8, 88.2, 109.3, 128.3, 128.5, 131.0, 137.0, 156.8, 160.4, 162.8, 163.8, 200.2; elemental analysis calcd (%) for $C_{16}H_{16}N_2O_2$ (268.32): C 71.62, H 6.01, N 10.44; found C 71.76, H 6.17, N 10.50.

1-[2-Phenyl-6-(4-propylsulfanyl[2,2′]bipyridinyl-6-yl)pyrimidin-4-yl]ethanone (11): A solution of potassium *tert*-butoxide (1.888 g, 16.82 mmol) in THF (10 mL, 3 × 5.0 mL rinse) was added by cannula to solution of **10** (2.242 g, 8.356 mmol) in THF (20.0 mL) at 0 °C. The enolate solution was stirred at 0 °C for 10 min then added by cannula to a solution of **6** (2.252 g, 8.002 mmol) in THF (20.0 mL, 3 × 5.0 mL rinse). The resulting purple solution was stirred at 0 °C for 4 h, then at RT for 13 h. Ammonium acetate (9.8 g) and glacial acetic acid (45 mL) were added, and the mixture was stirred at reflux for 90 min. After cooling to RT, the mixture was poured into H_2O (300 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed carefully with saturated $NaHCO_3$ (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated. The crude vinyl ether was partially purified by flash chromatography on neutral alumina (15 to 30% EtOAc/hexanes, then CH_2Cl_2 as eluant). The crude product was dissolved in acetone (38 mL) and aqueous HCl (2 N, 5.5 mL), and stirred at reflux for 45 min. After cooling to RT, the mixture was poured into $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (SiO_2, 30% EtOAc/hexanes) and recrystallized from hexane to give **11** (1.88 g, 58%) as clear, colorless plates. M.p. 166 °C; ^{1}H NMR: $\delta = 1.16$ (t, $J = 7.3$ Hz, 3H), 1.89 (sext, $J = 7.3$ Hz, 2H), 2.89 (s, 3H), 3.20 (t, $J = 7.3$ Hz, 2H), 7.37 (ddd, $J = 1.2$, 4.9, 7.6 Hz, 1H), 7.58 (m, 3H), 7.91 (dt, $J = 1.8$, 7.6 Hz, 1H), 8.46 (d, $J = 1.8$ Hz, 1H), 8.56 (d, $J = 1.8$ Hz, 1H), 8.68 (m, 4H), 8.92 (s, 1H); ^{13}C NMR: $\delta = 13.5$, 22.0, 25.8, 32.8, 111.2, 118.5, 119.0, 121.6, 124.1, 128.3, 128.6, 131.1, 136.9, 149.0, 152.1, 152.5, 155.2, 155.4, 160.3, 164.2, 165.0, 200.0; elemental analysis calcd (%) for $C_{25}H_{22}N_4OS$ (426.54): C 70.40, H 5.20, N 13.14; found C 70.18, H 4.93, N 12.93.

4,6-Bis-(3,3-bispropylsulfanylacryloyl)-2-phenylpyrimidine (12): Tributyl(1-ethoxyvinyl)stannane (16.00 g, 44.30 mmol) and $[Pd(PPh_3)_2Cl_2]$ (700 mg, 1.00 mmol) were added to a solution of **9** (4.54 g, 20.2 mmol) in DMF (45.0 mL). The solution was stirred at 80 °C for 20 h under N_2 atmosphere. Diethyl ether (100 mL) and an aqueous solution of KF (5.54 g in 45 mL H_2O) were added, and the mixture was stirred vigorously for 1 h at RT. The mixture was filtered and the solid was washed with additional diethyl ether (200 mL). The filtrate was washed with H_2O (200 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was dissolved in acetone (150 mL) and HCl (2 N, 30 mL), and stirred overnight at RT. The white precipitate was collected by filtration and washed with hexanes. The filtrate was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered, and concentrated to give a white solid that was combined with the white precipitate filtered previously. The combined material was recrystallized from hexanes to give 4,6-diacetyl-2-phenylpyrimidine (4.57 g, 94%) as white needles. M.p. 145 °C; ^{1}H NMR: $\delta = 2.81$ (s, 6H), 7.53 (m, 3H), 8.23 (s, 1H), 8.54 (m, 2H); ^{13}C NMR: $\delta = 25.6$, 110.6, 128.4, 128.8, 131.7, 136.0, 161.2, 165.1, 198.8; elemental analysis calcd (%) for $C_{14}H_{12}O_2N_2$ (240.26): C 69.99, H 5.03, N 11.66; found C 69.89, H 4.96, N 11.79.

4,6-Diacetyl-2-phenylpyrimidine (3.00 g, 12.5 mmol) was added portionwise to a mixture of dry DMSO (45 mL) and sodium hydride (2.19 g, 54.8 mmol). The red mixture was stirred at RT for 30 min then CS_2 (1.54 mL, 25.5 mmol) was slowly added. The solution was stirred for 15 min, and then propyl iodide (4.95 mL, 50.8 mmol) was added slowly. The resulting dark red solution was stirred at RT for 15 h. Ice water (150 mL) was added, and the resulting mixture was stirred for 10 min. The dark orange solid was filtered, washed with methanol, dried under high vacuum, and then recrystallized from EtOAc to give **12** (6.00 g, 86%) as red plates. M.p. 186 °C; ^{1}H NMR: $\delta = 1.09$, (t, $J = 7.3$ Hz, 6H), 1.18 (t, $J = 7.3$ Hz, 6H), 1.80 (sept, $J = 7.3$ Hz, 4H), 1.93 (sept, $J = 7.6$ Hz, 4H), 3.10 (t, $J = 7.6$ Hz, 4H), 3.16 (sept, $J = 7.3$ Hz, 4H), 7.52 (m, 3H), 7.80 (s, 2H), 8.54 (m, 2H), 8.60 (s, 1H); ^{13}C NMR: $\delta = 13.6$, 13.6, 21.2, 22.2, 33.4, 36.1, 108.1, 113.0, 127.9, 128.5, 131.0, 136.9, 163.1, 163.2, 169.0, 182.0; elemental analysis calcd (%) for $C_{28}H_{36}N_2O_2S_4$ (560.85): C 59.96, H 6.47, N 4.99; found C 60.18, H 6.48, N 5.05.

1-[6-(*tert*-Butyldiphenylsilanoxymethyl)-2-phenylpyrimidin-4-yl]ethanone (13): BBr_3 (1 M, 150 mL, in CH_2Cl_2) was added to a solution of **3** (10.01 g, 42.59 mmol) in CH_2Cl_2 (100 mL) cooled to −12 °C. The dark brown mixture was stirred and allowed to warm from at −12 °C to 0 °C over 3 h. The reaction was carefully quenched by addition of diethyl ether (200 mL), followed by H_2O (200 mL). The resulting mixture was stirred at RT for 2 h. The aqueous phase was separated and extracted with additional diethyl ether (2 × 200 mL). The combined organic phases were washed with saturated $NaHCO_3$ (200 mL) and brine (200 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by flash chromatography (30% EtOAc/hexanes) to give 4-chloro-6-hydroxymethyl-2-phenylpyrimidine (**3a**; 9.36 g, 99%) as a tan solid. M.p. 66 °C; ^{1}H NMR: $\delta = 3.38$ (t, $J = 5.5$ Hz, 1H), 4.77 (d, $J = 4.9$ Hz, 2H), 7.24 (s, 1H), 7.48 (m, 3H), 8.41 (m, 2H); ^{13}C NMR: $\delta = 63.6$, 115.3, 128.5, 128.6, 131.6, 135.7, 161.8, 164.6, 170.3; elemental analysis calcd (%) for $C_{11}H_9N_2OCl$ (220.66): C 59.88, H 4.11, N 12.70; found C 60.00, H 4.07, N 12.51.

Imidazole (2.864 g, 42.07 mmol), DMAP (1.804 g, 14.77 mmol), and *tert*-butyldiphenylsilyl chloride (13.2 mL, 49.7 mmol) were added to a solution of alcohol **3a** (9.197 g, 41.60 mmol) in CH_2Cl_2 (50 mL). The solution was stirred at RT for 24 h under N_2 atmosphere. The solution was diluted with CH_2Cl_2 (100 mL), and washed with H_2O (2 × 75 mL), saturated $NaHCO_3$ (75 mL), and brine (75 mL). The organic phase was dried, filtered, and concentrated. The crude material was purified by flash chromatography (5 to 10% EtOAc/hexanes) to give 6-*tert*-butyldiphenylsilanoxymethyl-4-chloro-2-phenylpyrimidine (**3b**; 19.1 g, 100%) as a white powder. M.p. 116 °C; ^{1}H NMR: $\delta = 1.20$ (s, 9H), 4.90 (2, H), 7.46 (m, 9H), 7.63 (s, 1H), 7.73 (m, 4H), 8.39 (m, 4H); ^{13}C NMR: $\delta = 19.3$, 26.9, 65.8, 115.2, 128.0, 128.5, 130.1, 131.3, 132.5, 135.5, 136.2, 162.4, 164.6, 172.0; elemental analysis calcd (%) for $C_{27}H_{27}N_2OClSi$ (459.06): C 70.64, H 5.93, N 6.10; found C 70.53, H 6.05, N 6.03.

Tributyl(1-ethoxyvinyl)stannane (15.37 g, 42.56 mmol) and $[Pd(PPh_3)_2Cl_2]$ (640 mg, 0.912 mmol) were added to a solution of chloropyrimidine **3b** (16.28 g, 35.46 mmol) in DMF (50.0 mL). The solution was stirred at 80 °C for 18 h under N_2. After cooling to 0 °C, diethyl ether (100 mL) and a solution of KF (5.94 g in 80 mL H_2O) were added. The mixture was stirred at RT for 45 min then filtered. The filtrate was washed with H_2O (2 × 100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was dissolved in acetone (100 mL) and cooled to 0 °C. An aqueous HCl solution (2 N, 18 mL) was added and the mixture was warmed to RT and stirred overnight. The mixture was the poured into $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (10% EtOAc/hexanes) to give **13** (14.94 g, 90%) as a white solid. M.p. 101 °C; ^{1}H NMR: $\delta = 1.26$ (s, 9H), 2.89 (s, 3H), 5.02 (s, 2H), 7.48 (m, 9H), 7.80 (m, 4H), 8.22 (s, 1H), 8.52 (m, 2H); ^{13}C NMR: $\delta = 19.2$, 25.7, 26.8, 66.2, 110.8, 127.8, 128.2, 128.5, 129.9, 131.0, 132.7, 135.5, 136.8, 159.8, 163.8, 172.4, 200.0; elemental analysis calcd (%) for $C_{29}H_{30}N_2O_2Si$ (466.65): C 74.64, H 6.48, N 6.00; found C 74.86, H 6.37, N 6.07.

1-{6-{-6-[6-(*tert*-Butyldiphenylsilanyloxymethyl)-2-phenylpyrimidin-4-yl]-4-propylsulfanylpyridin-2-yl}-2-phenylpyrimidin-4-yl}-3,3-bispropylsulfanylpropenone (14): A solution of KOtBu (1.16 g, 10.4 mmol) in THF (10.0 mL; 3 × 5 mL rinse) was added by cannula to a 0 °C solution of **13** (2.41 g, 5.16 mmol) in THF (15.0 mL). The enolate solution was stirred for 10 min then added by cannula to a 0 °C solution of **12** (5.76 g, 10.3 mmol) in THF (30 mL). The purple solution was stirred at 0 °C for 5 min then at RT for 18 h. Ammonium acetate (58 g) and AcOH (58 mL) were added, and the solution was stirred at 80 °C for 100 min. After cooling to RT, the mixture was poured into NaOH (2 N, 480 mL) at 0 °C then extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with $NaHCO_3$ (200 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (70% CH_2Cl_2/hexane to elute product followed by EtOAc to remove unreacted **12**). Compound **14** was purified further by recrystallization from EtOAc to give orange plates (3.05g, 61%). M.p. 168 °C; ^{1}H NMR: $\delta = 1.10$ (t, $J = 7.3$ Hz, 3H), 1.20 (t, $J = 7.3$ Hz, 3H), 1.21 (t, $J = 7.3$ Hz, 3H), 1.30 (s, 9H), 1.78 (sext, $J = 7.3$ Hz, 2H), 1.96 (sext, $J = 7.3$ Hz, 2H), 1.98 (sext, $J = 7.3$ Hz, 2H), 3.11 (t, $J = 7.3$ Hz, 2H), 3.20 (t, $J = 7.6$ Hz, 2H), 3.21 (t, $J = 7.6$ Hz, 2H), 5.05 (s, 2H), 7.41 (m, 6H), 7.52 (m, 3H), 7.55 (m, 3H), 7.85 (m 5H), 8.62 (m, 6H), 8.70 (s, 1H), 9.06 (s, 1H); ^{13}C NMR: $\delta = 13.6$, 13.6, 13.7, 19.3, 21.4, 22.2, 22.3, 26.9, 32.9, 33.4, 36.2, 66.5, 108.6, 111.9, 112.7, 119.8, 127.7, 128.2, 128.3, 128.4, 128.5, 129.7, 130.5, 130.8, 133.2, 135.8, 137.4, 137.8, 152.1, 153.6, 154.2, 162.7, 162.8, 163.4, 163.5, 164.6, 168.0, 171.1, 182.4; FAB-MS: *m/z*: 932.3 ($C_{54}H_{57}N_5O_2S_3Si$ requires 932.354); elemental analysis calcd (%) for $C_{54}H_{57}N_5O_2S_3Si \cdot 0.8\,C_6H_6$ (994.86): C 70.99, H 6.26, N 7.04; found C 71.39, H 6.35, N, 7.42. The compound was dried azeotropically by evaporation of a benzene solution.

{2-Phenyl-6-{6-{2-phenyl-6-{6-[2-phenyl-6-(4-propylsulfanyl[2,2′]bipyridinyl-6-yl)pyrimidin-4-yl]-4-propylsulfanylpyridin-2-yl}pyrimidin-4-yl}-4-propylsulfanylpyridin-2-yl}pyrimidin-4-yl}methanol (15): NaH (152 mg, 3.80 mmol; 60% dispersion in mineral oil) was added to a 0 °C solution of **11** (1.46 g, 3.42 mmol) in THF (10 mL). After the mixture was stirred at RT for 5 min, a solution of **14** (2.61 g, 3.05 mmol) in THF (15.0 mL; 3 × 2.0 mL rinse) was added by cannula. The resulting solution was stirred at 50 °C for 16 h under N_2 atmosphere. Ammonium acetate (4.51 g) and AcOH (15.0 mL) were added, and the mixture was stirred at 80 °C for 1 h. After cooling to RT, the mixture was poured into cold NaOH (2 N, 80 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered, and concentrated. The crude mixture was dissolved in acetone and left to stand for 1 h at 4 °C. The product was obtained by filtration and washed with cold acetone. The compound was further purified by flash chromatography (70% CH_2Cl_2/hexanes to 100% CH_2Cl_2 to 100% $CHCl_3$) to give protected compound **15a** (2.35 g, 61%) as light yellow powder. M.p. 228 °C; ^{1}H NMR (C_6D_6): $\delta = 0.80$ (s, 9H), 0.86 (t, $J = 7.3$ Hz, 3H), 0.95 (t, $J = 7.0$ Hz, 6H), 1.62 (sext, $J = 7.3$ Hz, 6H), 2.72 (t, $J = 7.3$ Hz, 2H), 2.80 (t, $J = 7.0$ Hz, 2H), 2.82 (t, $J = 7.3$ Hz, 2H), 4.38 (s, 2H), 6.36 (br t, $J = 4.6$ Hz, 1H), 6.66 (dt, $J = 1.8$, 6.1 Hz, 1H), 6.98 (m, 6H), 7.42 (m, 15H), 8.01 (d, $J = 4.0$ Hz, 1H), 8.36 (d, $J = 1.5$ Hz, 1H), 8.40 (d, $J = 1.5$ Hz, 1H), 8.62 (s, 1H), 8.68 (163.m, 7H), 8.95 (m, 4H), 9.94 (s, 1H), 10.02 (s, 1H); ^{13}C NMR (C_6D_6): $\delta = 13.6$, 18.7, 22.0, 22.2, 22.3, 26.4, 32.8, 32.9, 33.0, 65.7, 111.7, 112.6, 112.7, 118.2, 118.5, 119.4, 119.5, 119.6, 120.9, 123.3, 127.4, 127.4, 127.5, 128.2, 128.2, 128.4, 128.6, 129.4, 130.2, 130.6, 130.8, 132.8, 135.1, 135.2, 135.2, 135.3, 135.5, 137.8, 137.9, 148.0, 151.5, 151.7, 152.1, 153.0, 153.6, 153.8, 153.9, 154.2, 154.3, 154.9, 162.3, 162.6, 163.5, 163.6, 163.9, 164.1, 164.1, 170.4; FAB-MS: *m/z*: 1263.4 ($C_{76}H_{70}N_{10}OS_3Si$ requires 1263.7372); elemental analysis calcd (%) for $C_{76}H_{70}S_3N_{10}OS_3Si$ (1263.72): C 72.23, H 5.58, N 11.08; found C 72.35, H 5.51, N 11.06.

Bu_4NF (1 M, 2.00 mL, 2.20 mmol; solution in THF) was added to a solution of the protected helix **15a** (2.05 g, 1.62 mmol) in THF (20 mL). The solution was stirred at RT for 1.5 h, and then poured into saturated $NaHCO_3$ (80 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with brine (60 mL), dried over $MgSO_4$, filtered, and concentrated. The crude alcohol was purified by flash chromatography (80% EtOAc/hexanes to 100% EtOAc) to give **15** (1.66 g, 100%) as a white solid. M.p. 247 °C; ^{1}H NMR: $\delta = 1.17$ (t, $J = 7.3$ Hz, 3H), 1.23 (t, $J = 7.3$ Hz, 3H), 1.24 (t, $J = 7.3$ Hz, 3H), 1.93 (sext, $J = 7.3$ Hz, 6H), 3.15 (t, $J = 7.6$ Hz, 2H), 3.22 (t, $J = 7.0$ Hz, 4H), 3.30 (t, $J = 5.2$ Hz, 1H), 3.91 (d, $J = 5.2$ Hz, 2H), 6.71 (m, 2H), 7.56 (m, 9H), 8.08 (m, 1H), 8.13 (m, 2H), 8.22 (m, 1H), 8.41 (m, 3H), 8.57 (d, $J = 1.8$ Hz, 1H), 8.59 (d, $J = 1.8$ Hz, 1H), 8.63 (m, 2H), 8.72 (m, 4H), 9.64 (s, 1H), 9.66 (s, 1H); ^{13}C NMR: $\delta = 13.6$, 21.8, 22.0, 22.1, 32.6, 63.1, 111.0, 111.2, 118.3, 118.4, 118.8, 119.0, 119.0, 119.2, 120.8, 123.0, 128.1, 128.2, 130.2, 130.4, 134.7, 135.2, 137.4, 137.5, 147.7, 151.4, 151.5, 151.9, 152.7, 152.8, 152.9, 153.0, 153.1, 153.9, 154.6, 161.0, 162.9, 163.1, 163.2, 168.9; elemental analysis calcd (%) for $C_{60}H_{52}N_{10}OS_3$ (1025.32): C 70.29, H 5.11, N 13.66; found C 70.45, H 4.97, N 13.42.

2-Phenyl-6-{6-{2-phenyl-6-{6-[2-phenyl-6-(4-propylsulfanyl[2,2′]bipyridinyl-6-yl)pyrimidin-4-yl]-4-propylsulfanylpyridin-2-yl}pyrimidin-4-yl}-4-propylsulfanylpyridin-2-yl}pyrimidin-4-carbaldehyde (16): DMSO (0.100 mL, 1.41 mmol) was added to a solution of oxalyl chloride (0.06 mL, 0.69 mmol) in CH_2Cl_2 (1.0 mL) at −78 °C. After stirring for 5 min, a solution of **15** (296 mg, 0.288 mmol) in CH_2Cl_2 (1.0 mL; 3 × 0.5 mL rinse) was added by cannula. The resulting solution was stirred at −78 °C for 30 min and then at −45 °C for 30 min. Triethylamine (0.90 mL) was added, and the mixture was warmed to RT. The solution was poured into saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was boiled in acetone and filtered to yield **16** (272 mg, 92%) as a white solid. M.p. 275 °C; ^{1}H NMR: $\delta = 1.20$ (t, $J = 7.3$ Hz, 3H), 1.23 (t, $J = 7.3$ Hz, 6H), 1.94 (m, 6H), 3.15 (t, $J = 7.6$ Hz, 4H), 3.19 (t, $J = 7.3$ Hz, 2H), 6.65 (m, 2H), 7.58 (m, 9H), 7.89 (m, 1H), 8.01 (d, $J = 1.8$ Hz, 1H), 8.13 (m, 1H), 8.21 (d, $J = 1.8$ Hz, 1H), 8.34 (s, 1H), 8.40 (d, $J = 1.8$ Hz, 2H), 8.46 (d, $J = 1.8$ Hz, 2H), 8.52 (m, 2H), 8.67 (m, 4H), 9.16 (s, 1H), 9.56 (s, 1H), 9.66 (s, 1H); ^{13}C NMR: $\delta = 13.6$, 13.8, 21.9, 22.0, 22.2, 32.7, 32.7, 110.7, 111.8, 112.0, 117.9, 118.2, 118.8, 119.0, 119.2, 120.8, 123.2, 128.3, 130.4, 130.5, 130.7, 135.3, 136.9, 137.5, 137.9, 147.4, 151.1, 151.5, 151.6, 152.2, 152.5, 152.8, 153.2, 153.9, 154.0, 158.2, 162.6, 162.8, 163.1, 163.3, 163.3, 163.6, 163.8, 190.2; HRMS (FAB-MS) calcd for $C_{60}H_{50}N_{10}OS_3$ 1023.3409, found 1023.3409; FAB-MS: *m/z* (%): 1023.5 (100) $[M+H]^+$.

4,6-Bis-{2-phenyl-6-{6-{2-phenyl-6-{6-[2-phenyl-6-(4-propylsulfanyl[2,2′]-bipyridinyl-6-yl)pyrimidin-4-yl]-4-propylsulfanylpyridin-2-yl}-4-propylsulfanylpyridin-2-yl}pyrimidin-4-ylmethylene}hydrazino-2-phenylpyrimidine (2): Aldehyde **16** (50.1 mg, 0.0489 mmol) and bishydrazine **17** (5.3 mg, 0.024 mmol) were dissolved in a 1:1 mixture of EtOH/$CHCl_3$ (2.0 mL). The solution was stirred at reflux for 3 h in the presence of 4 Å sieves. The solution was filtered and concentrated to give **2** (52 mg, quantitative) as a light yellow solid. M.p. >280 °C; ^{1}H NMR ([D$_8$]THF): $\delta = 1.06$ (t, $J =$

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7.3 Hz, 6H), 1.24 (t, $J = 7.3$ Hz, 6H), 1.27 (t, $J = 7.3$ Hz, 6H), 1.82 (m, $J = 7.3$ Hz, 4H), 1.95 (m, $J = 7.3$ Hz, 8H), 3.10 (m, 12H), 6.30 (dt, $J = 1.5$, 7.6 Hz, 2H), 6.44 (m, 12H), 6.68 (s, 2H), 6.93 (m, 9H), 7.16 (m, 1H), 7.51 (m, 12H), 7.78 (m, 4H), 7.83 (d, $J = 1.5$ Hz, 2H), 7.91 (d, $J = 7.9$ Hz, 2H), 8.11 (m, 8H), 8.28 (d, $J = 1.5$ Hz, 2H), 8.34 (m, 6H), 8.41 (m, 4H), 8.46 (s, 2H), 9.46 (s, 2H), 9.54 (s, 2H), 9.63 (s, 2H), 10.84 (s, 2H); elemental analysis calcd (%) for $C_{130}H_{108}N_{26}S_6 \cdot 4H_20$ (2298.88): C 67.92, H 5.08, N 15.84; found C 68.05, H 4.84, N 15.81.

Crystal structure data for 1: Single crystals of compound **1** [$C_{58}H_{48}S_2N_{14} \cdot (C_4H_8O)$] were grown from tetrahydrofuran/acetone. The crystals were placed in oil, and a single, light yellow crystal of dimensions $0.22 \times 0.12 \times 0.12$ mm was selected, mounted on a glass fiber, and placed in a low-temperature N_2 stream. X-ray diffraction data for **1** were collected on a Nonius-KappaCCD diffractometer with a graphite monochromatized $Mo_{K\alpha}$ radiation ($\lambda = 0.71071$ Å), phi scans, at 173 K. The unit cell was orthorhombic with a space group of *Pbcn*. Cell dimensions: $a = 57.380(2)$, $b = 9.200(2)$, $c = 21.490(4)$ Å, α, β, $\gamma = 90°$, $V = 11344(3)$ Å^3, and $Z = 8$ ($M_w = 1077.34$, $\rho = 1.257$ g cm^{-3}). Reflections were collected from $2.37 \leq \theta \leq 26.50$ for a total of 12337 of which 2947 were unique ($R_{int} = 0.058$); number of parameters = 689. Final R factors were $R1 = 0.1169$ (based on observed data), w$R2 = 0.3021$ (based on all data), GOF = 1.051, maximal residual electron density = 0.550 e Å^{-3}. The structure solution of compound **1** were solved using direct methods and refined (based on F^2 using all independent data) by full-matrix least-squares methods (Siemens SHELXTL 96 V. 5.02). Hydrogen atoms were included at calculated positions by using a riding model.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-138214. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[1] See for instance: *Acc. Chem. Res.* **1998**, *31*, 697–780, special issue on protein folding.

[2] See for instance: a) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173; b) J. S. Nowick, *Acc. Chem. Res.* **1999**, *32*, 287.

[3] For recent reviews see: a) C. Piguet, G. Bernardinelli, G. Hopfgartner, *Chem. Rev.* **1997**, *97*, 2005; b) A. E. Rowan, R. J. M. Nolte, *Angew. Chem.* **1998**, *110*, 65; *Angew. Chem. Int. Ed.* **1998**, *37*, 63.

[4] For recent examples, see: a) A. Tanatani, H. Kagechika, I. Azumaya, R. Fukutomi, Y. Ito, K. Yamaguchi, K. Shudo, *Tetrahedron Lett.* **1997**, *38*, 4425; b) T. Hasegawa, S. Kondoh, K. Matsuura, K. Kobayashi, *Macromol.* **1999**, *32*, 6595; b) H. Nakako, R. Nomura, M. Tabata, T. Masuda, *Macromol.* **1999**, *32*, 2861; c) D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1999**, *121*, 6206;.

[5] a) T. Hintermann, K. Gademann, B. Jaun, D. Seebach, *Helv. Chim. Acta*. **1998**, *81*, 983; b) S. Hanessian, X. Luo, R. Schaum, *Tetrahedron Lett.* **1999**, *40*, 4925.

[6] R. B. Prince, J. G. Saven, P. G. Wolynes, J. S. Moore, *J. Am. Chem. Soc.* **1999**, *121*, 3114.

[7] J.-M. Lehn *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, **1995**.

[8] For some recent examples see: a) H.-P. Wu, C. Janiak, L. Uehlin, P. Klüfers, P. Mayer, *Chem. Commun.* **1998**, 2637; b) G. Baum, E. C. Constable, D. Fenske, C. E. Housecroft, T. Kulke, *Chem. Commun.* **1999**, 195; c) T. B. Norsten, R. Mc Donald, N. R. Branda, *Chem. Commun.* **1999**, 719; M. J. Hannon, C. L. Painting, N. W. Alcock, *Chem. Commun.* **1999**, 2023; D. L. Calder, K. R. Raymond, *Acc. Chem. Res.* **1999**, *32*, 975; M. Albrecht, *J. Inclusion Phenom. Macrocyclic Chem.* **2000**, *36*, 127.

[9] a) G. S. Hanan, J.-M. Lehn, N. Kirytsakas, J. Fischer, *J. Chem. Soc. Chem. Commun*. **1995**, 765; b) G. S. Hanan, U. S. Schubert, D. Volkmer, E. Rivière, J.-M. Lehn, N. Krytsakas, J. Fischer, *Can. J. Chem*. **1997**, *75*, 169; c) D. M. Bassani, J.-M. Lehn, G. Baum, D. Fenske, *Angew. Chem*. **1997**, *109*, 1931; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1845; d) D. M. Bassani, J.-M. Lehn, *Bull. Soc. Chim. Fr*. **1997**, *134*, 897; e) M. Ohkita, J.-M. Lehn, G. Baum, D. Fenske *Chem. Eur. J.* **1999**, *5*, 3471; f) L. Cuccia, J.-M. Lehn, J.-C. Homo, M. Schmutz, *Angew. Chem*. **2000**, *112*, 239; *Angew. Chem. Int. Ed.* **2000**, *39*, 233.

[10] M. Kosugi, T. Sumiya, Y. Obara, M. Suzuki, H. Sano, T. Migita *Bull. Chem. Soc. Jpn*. **1987**, *60*, 767.

[11] a) K. T. Potts, M. J. Cipullo, P. Ralli, G. Theodoridis *J. Org. Chem*. **1982**, *47*, 1982; b) K. T. Potts, P. A. Winslow *J. Org. Chem*. **1985**, *50*, 5405; c) K. T. Potts *Bull. Soc. Chim. Belg*. **1990**, *99*, 741.

[12] For more detailed discussion of this anisotropic upfield shift see ref. [9e].

[13] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem*. **1978**, *43*, 2923.

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