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Synthesis of Heterocycles Containing Two Cytosine or Two Guanine Base-Pairing Sites. Novel Tectons for Self-Assembly[†]

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Abstract—The synthesis of **1** and **2** is described, as is the X-ray structure of **1**. Tecton **1** contains two DAA hydrogen bonding sites (cytosine-like), while **2** contains two DDA sites (guanosine-like). Tectons **1** and **2** were designed to self-assemble into a helical superstructure. Self-recognition of **1** occurs in the solid state with a novel inclusion of dimethylacetamide solvent. Copyright © 1996 Elsevier Science Ltd

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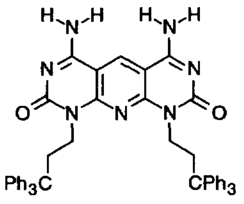
Introduction

The central role that self-assembly plays in the organization of biological systems has inspired organic chemists to develop abiotic structures that spontaneously form novel supramolecular architectures in solution, mesophases, and the solid state.[1] Beyond shedding light on the fundamental aspects of natural assembly processes, some of these studies may be useful in developing new materials and nanoscale devices. With regard to specific architectures, the helical assembly seen in many viral capsids provides one of the most inspirational examples of biological self-assembly.[2]

We have been interested in compounds that can assemble into similar structures in solution or in the solid state, and thus contain voids for encapsulating other molecules.[3] As part of this effort a pyrido[4,3-*g*]quinolinedione was synthesized and found to form a very robust cyclic trimer.[3a] This finding supported the idea that disc- and washer-shaped structures could be assembled using hydrogen bonding.[3,4] However, this simple assembly lacked a sizeable internal hole/void, and the constituent DA·AD hydrogen bonding motif lacks the strength and geometrical control necessary for the specific formation of larger nano- and mesoscopic assemblies.[3a] As we and others have noted, the DDA·AAD hydrogen bonding motif of the G-C base-pair is very strong and specific with regard to directionality.[5-7] Herein the synthesis of novel 'tectons'[8] **1** and **2** containing two DDA or two AAD hydrogen bonding sites is described,[9] along with the novel X-ray structure of **1**.



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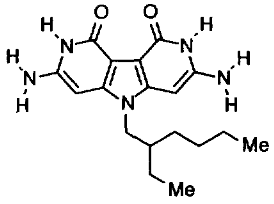

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Results and Discussion

Initially, tecton **3**, a close analogue of **1** with two cytosine units fused to a central phenyl ring was chosen as the target. Its attempted synthesis is outlined in Scheme 1. Treatment of tetrachloroisophthalonitrile (**4**) with butylamine in refluxing benzene gave the diamine product **5** in 30% yield.[10] Selective reduction with palladium on carbon and sodium hypophosphite occurred smoothly to produce tetrasubstituted benzene **6** in 96% yield. Although there were several reported methods of converting *o*-alkylaminobenzonitriles to 1-alkyl-4-amino-2-quinazolones,[11] the low reactivity of the amino groups in **6** proved to be problematic. For example, upon treatment of **6** with phosgene in refluxing toluene, followed by addition of ammonia, only one of the amino groups reacted. The structure of the product was not firmly established, but spectral data are consistent with quinazoline **8** or its open-chain isomer **7**.

Tecton **1** is functionally equivalent to **3**, but contains two cytosine units fused to a central pyridine ring. Its synthesis is outlined in Scheme 2. Readily available

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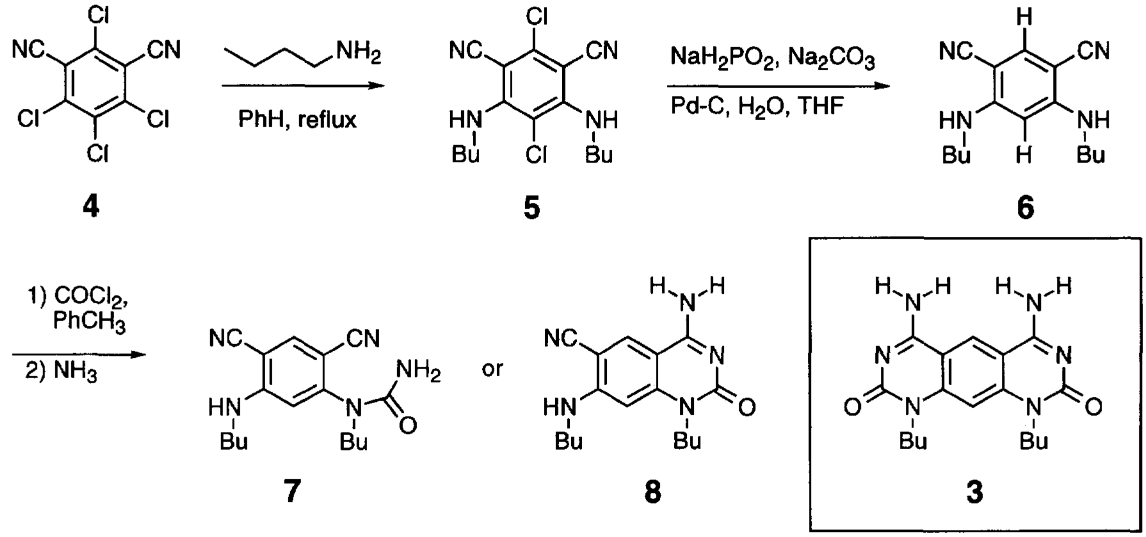
[†] In honor of Professor Sir A. R. Battersby and Professor A. I. Scott, the 1995 Tetrahedron Prize recipients, and in gratitude for A. R. Battersby's inspiring mentorship of P.M.P. (1990–1992) and S.C.Z. (1984–1985).

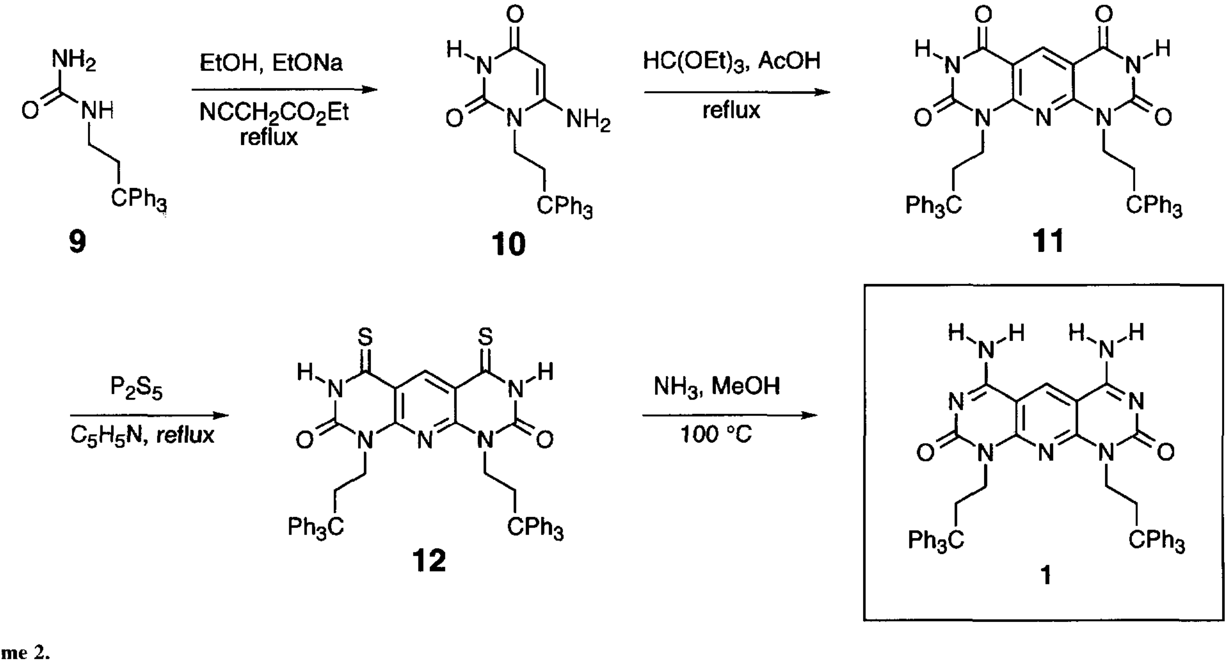


Scheme 1.

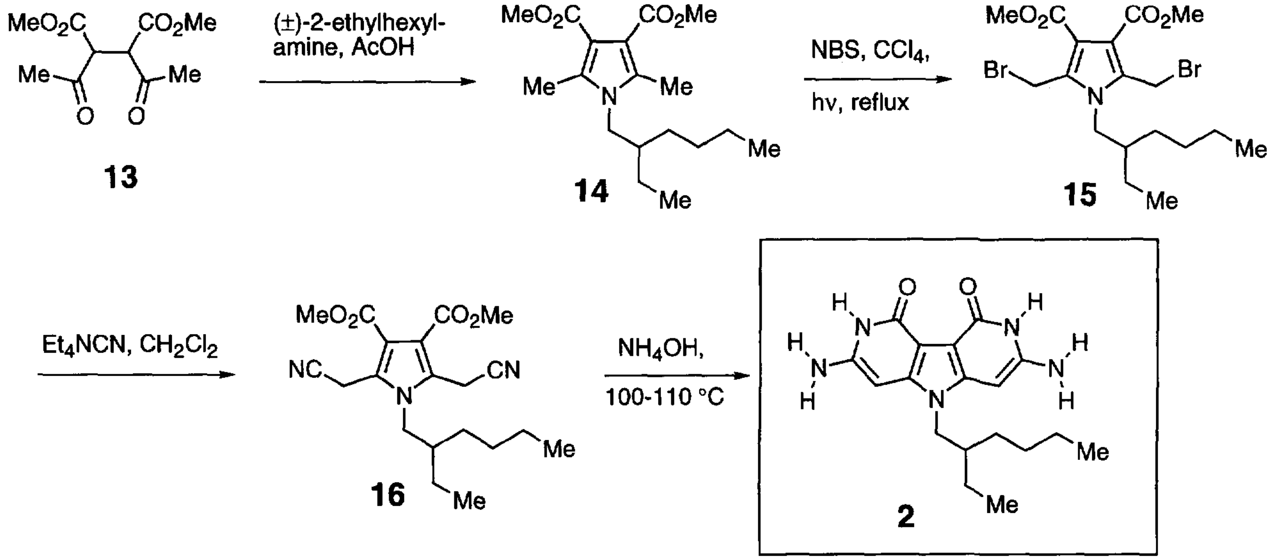
3,3,3-triphenyl-propylamine[12] was converted to urea **9** by treatment with cyanogen bromide (ether, 0 °C to room temperature) followed by hydrolysis (3 N HCl, 60 °C; 48% yield). Urea **9** condensed with ethyl cyanoacetate to produce aminouracil **10** in 92% yield, which self-coupled upon treatment with triethyl orthoformate in acetic acid to form bis-uracil **11** in 59% yield.[13] Regioselective thionation[14] at C-4 and C-6 with phosphorous pentasulfide afforded **12** in 83% yield. Compound **1** was obtained from **12** in 97% yield by treatment with methanolic ammonia in a sealed tube.' Similarly, 4,6-*N*-alkyl derivatives of **1** could be prepared by reaction of **12** with primary amines.

The preparation of **2** began with the condensation of dimethyl diacetylsuccinate[15] (**13**) and racemic 2-ethylhexylamine to form pyrrole **14** in 97% yield (Scheme 3).[16] Bromination with *N*-bromosuccinimide gave dibromide **15** in good yield and treatment with tetraethylammonium cyanide[17] smoothly converted **15** into dinitrile **16** (64% yield for two steps). The desired 'bis-guanine' **2** was obtained in 22% yield upon heating dinitrile **16** with 30% aqueous ammonium hydroxide in a sealed tube.[18]

The syntheses outlined in Schemes 2 and 3 are sufficiently flexible to allow a variety of substituents to be incorporated, ultimately allowing control over the size and morphology of the putative aggregates (vide infra). For example, the 2-ethylhexyl substituent in **2** increased its solubility in organic solvents and may induce the formation of an optically active helix when



Scheme 2.



Scheme 3.

nonracemic. The triphenylpropyl substituent in tecton **1** enhanced its solubility in organic solvents,[19] and increased its crystallinity over corresponding straight-chain alkane substituted compounds. Indeed, **1** readily crystallized from *N*,*N*-dimethylacetamide (DMA) as a 1 : 1 solvate, and its structure was determined by X-ray analysis.[20]

As seen in Figures 1(a) and 1(b), the two N—H groups of **1** converge on the carbonyl oxygen atom of the DMA, although the hydrogen bonds are directed more to the *p*-system than to the traditional carbonyl oxygen lone-pairs.[21] The donor–acceptor (DA) site is self-complementary and each molecule forms two hydrogen bonds to two adjacent molecules forming a ribbon [Fig. 1(c)].

In the tautomeric forms and conformations shown, tectons **1** and **2** are complementary, but cannot form a closed structure. As seen schematically in Figure 2, **1** and **2** may noncovalently assemble into a hydrogen bonded, helical aggregate. The use of substituted amines in the **12**→**1** conversion would provide 'endocyclic functionality' (X group in Fig. 2) to control the internal diameter and chemical nature of the resultant assembly. On the other hand, the ability of **1** to complex DMA in the solid state suggests that assemblies derived from **1** and **2** may be effective agents for encapsulating carbonyl containing guests. These possibilities are under investigation and the results will be reported in due course.

Experimental

All reactions were carried out under a dry nitrogen atmosphere. Tetrahydrofuran (THF), benzene, and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Methanol was distilled from magnesium turnings prior to use. Triethylamine was distilled from calcium hydride prior to use. *N*-Bromosuccinimide was recrystallized from water. Tetrachloroisophthalonitrile (**4**) was purchased from TCI America, Inc. All other solvents and reagents were of reagent-

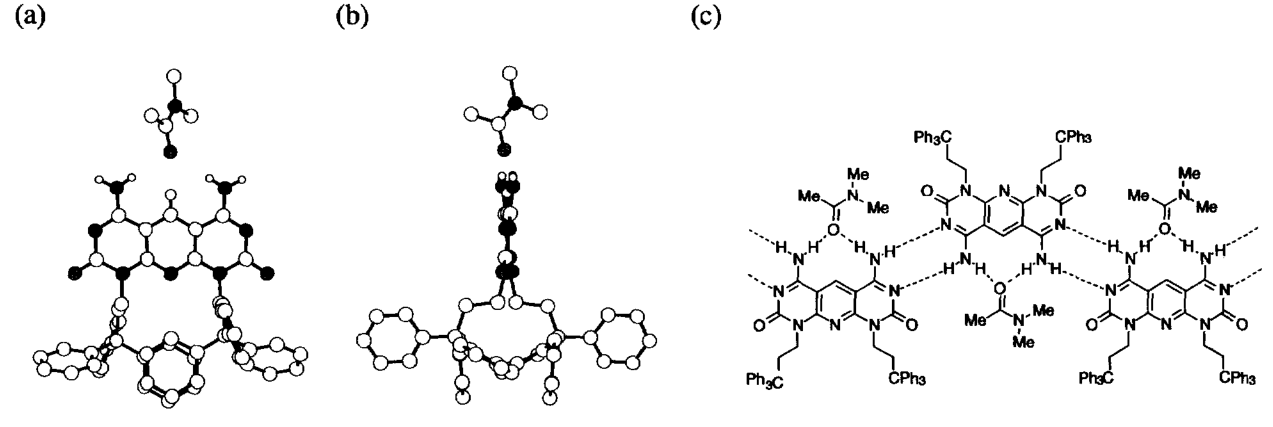


Figure 1. (a) Top; (b) side, views of X-ray structure of 1 · DMA; and (c) solid-state ribbon formed by 1 · DMA.

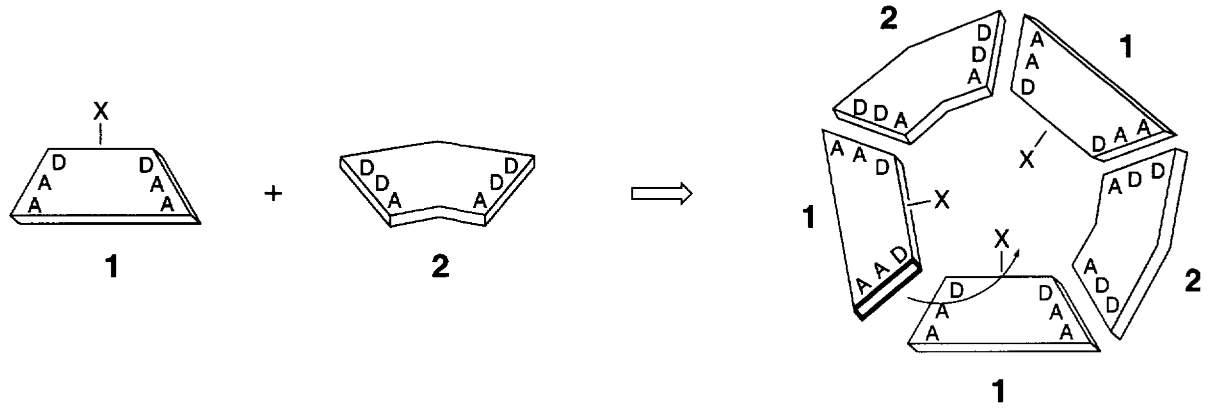


Figure 2. Schematic representation of hydrogen bonded, helical assembly from **1** and **2**.

grade quality and used without further purification. Analytical TLC was performed on 0.2 μm silica 60 coated plastic or glass plates (EM Science) with F-254 indicator. Flash chromatography was performed on Merck 40–63 mm silica gel.

^{1}H and ^{13}C NMR spectra were recorded on a General Electric QE-300 instrument (300 MHz, ^{1}H; 75 MHz, ^{13}C) in chloroform-*d* ($CDCl_3$) unless otherwise stated. Chemical shifts are reported in ppm, referenced to tetramethylsilane (0.00 ppm) or residual protio solvent (7.26 ppm). Coupling constants are reported in Hz. MS were obtained on a Finnigan-MAT CH-5 (EI) or ZAB-SE (FAB) spectrometer. Elemental analyses were performed at the University of Illinois, School of Chemical Sciences. Melting points were measured on either a Thomas–Hoover or a Reichert hot stage melting point apparatus and are uncorrected.

4,6-Di(butylamino)-2,5-dichloro-1,3-benzonitrile (5). To a suspension of 8.60 g (32.3 mmol) of tetrachloroisophthalonitrile (4) in 100 mL of benzene was added 24 mL of butylamine and 0.6 mL of triethylamine. The mixture was refluxed for 40 h, cooled to room temperature, filtered, and the solvent evaporated to give a yellow solid. The solid was washed extensively with ether to give 3.30 g (30%) of **5** as a pale-yellow powder: mp 114–115 °C; ^{1}H NMR: δ 4.99 (t, $J=4.9$, 2H, NH), 3.77–3.70 (m, 4H, NCH_2), 1.71–1.62 (m, 4H, CH_2), 1.44 (sextet, $J=J'=7.3$, 4H, $\underline{CH_2}CH_3$), 0.97 (t, $J=7.3$, 6H, CH_3); ^{13}C NMR: δ 148.6, 144.6, 115.7, 102.7, 88.3, 45.4, 32.5, 19.7, 13.7; MS (EI, 70 eV): *m/z* (relative intensity) 338 (M^+, 19), 295 (100). Anal. calcd for $C_{16}H_{20}Cl_2N_2$: C, 56.64; H, 5.94; N, 16.51; Cl, 20.90. Found: C, 56.74; H, 6.00; N, 16.42; Cl, 20.85.

4,6-Di(butylamino)1,3-benzonitrile (6). To a solution of 0.34 g (1.0 mmol) of **5** in THF (20 mL) was added, 0.24 g (2.2 mmol) of sodium carbonate and 0.05 g of 10% palladium on carbon. A solution of 0.34 g (2.2 mmol) of sodium hypophosphite in 2 mL of water was slowly added to the reaction mixture. The reaction was monitored by TLC (additional sodium carbonate and sodium hypophosphite were added if needed to complete the reaction) until complete formation of the product. The mixture was filtered and the filtrate was extracted thoroughly with dichloromethane. The combined organic extracts were dried over sodium sulfate and the sovent removed as reduced pressure to give 0.26 g (96%) of **6** as a white solid: mp 128–130 °C; ^{1}H NMR: δ 7.44 (s, 1H, ArH), 5.64 (s, 1H, ArH), 4.81 (t, 2H, NH), 3.18 (m, 4H, NCH_2), 1.66 (m, 4H, CH_2), 1.44 (m, 4H, CH_2), 0.97 (t, 6H, CH_3); ^{13}C NMR: δ 153.0, 138.2, 117.0, 89.0, 85.7, 42.6, 32.2, 19.9, 13.5. MS (EI, 70 eV): *m/z* (relative intensity) 270 (M^+, 21), 228 (16), 227 (100). Anal. calcd for $C_{16}H_{22}N_4$: C, 71.08; H, 8.20; N, 20.72. Found : C, 71.15; H, 8.22; N, 20.73.

***N*-(3,3,3-Triphenylpropyl)urea (9).** To a suspension of 8 g (28 mmol) of 3,3,3-triphenylpropylamine[12] in 40 mL of ether at 0 °C was slowly added 3.54 g (33 mmol) of cyanogen bromide in ether, and the resulting mixture was stirred at room temperature for 15 h. A white precipitate (triphenylpropylammonium hydrobromide; 3.8 g, 74% unreacted starting material) separated and was filtered and washed thoroughly with ethyl acetate (Note: this material was recycled for use in later experiments). The filtrate was diluted with 50 mL of ethyl acetate and the organic fraction was washed twice with 20 mL of dilute aqueous acetic acid, 20 mL of water (adjusted to pH 7 with ammonia), and dried over sodium sulfate. The solvent was removed at reduced pressure to give a white foam, which was dissolved in 80 mL of 3 N aqueous hydrochloric acid and heated at 60 °C for 16 h. The mixture was cooled, basicified with concd ammonium hydroxide and extracted three times with 50 mL of ethyl acetate. The combined organic layers were washed twice with 20 mL of water and dried over sodium sulfate. The solvent was removed under reduced pressure to give a white-oily solid that was taken into a large volume of hot ethyl acetate. Hexane was added and the solution was allowed to cool giving 2.2 g (48%) of urea **9** as colorless needles: mp 201–203 °C; ^{1}H NMR: δ ($CDCl_3$:DMSO-d_6) 7.26–7.07 (15H, m, CPh_3), 5.14 (1H, br, NH), 4.51 (2H, s, NH_2), 2.85–2.70 (4H, m, CH_2CH_2); Anal. calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.70; H, 6.65; N, 8.38.

6-Amino-1-(3,3,3-triphenylpropyl)-2,4(1*H*,3*H*)-pyrimidinedione (10). To a stirred solution of sodium ethoxide in ethanol obtained from 0.38 g (16.4 mmol) of sodium in 40 mL of ethanol was added 2.7 g (8.2 mmol) of *N*-(3,3,3-triphenylpropyl)urea (**9**) and, dropwise, 0.87 mL (8.2 mmol) of ethyl cyanoacetate. The resulting mixture was heated to reflux for 20 h. The mixture was cooled and the ethanol was removed under reduced pressure. The residue was dissolved in 100 mL of 5% (v/v) methanol–dichloromethane, washed twice with 30 mL of dilute aqueous hydrochloric acid, twice with 30 mL of a saturated aqueous sodium chloride solution, and dried over sodium sulfate. The solvent was removed at reduced pressure to give 3 g (92%) of **10** as a white powder: mp 266–268 °C; ^{1}H NMR: δ (DMSO-d_6) 10.45 (1H, s, NH), 7.34–7.17 (15H, m, CPh_3), 5.86 (2H, s, NH_2), 4.61 (1H, s, CH), 3.29–3.23 (2H, m, CH_2), 2.87–2.82 (2H, m, CH_2). HRMS calcd for $C_{25}H_{23}N_3O_2$: 397.1790; found: 397.1789.

1,9-Di(3,3,3-triphenylpropyl)pyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone (11). A mixture of 0.5 g (1.26 mmol) of **10**, 0.5 mL (3.0 mmol) of triethylorthoformate, and 5 mL of glacial acetic acid was heated at reflux. The mixture, which became homogeneous within 5 min, was refluxed for 2 h and allowed to cool. The precipitate was filtered, washed with acetic acid, and dried at reduced pressure in an Abderhalden drying pistol (toluene) to afford 0.29 g (59%) of **11** as a cream–white powder: mp 327 °C; ^{1}H NMR (DMSO-d_6): δ 11.8 (2H, br, 2NH), 8.56 (1H, s, ArH), 7.16–7.12 (30H, m, $2CPh_3$), 3.94 (4H, br, $2CH_2$), 2.81–2.79 (4H, br, $2CH_2$), 1.90 (3H, s, CH_3CO_2H); HRMS calcd for $C_{51}H_{41}N_5O_4$: 787.3159; found: 787.3163. Anal. calcd for $C_{51}H_{41}N_5O_4 \cdot CH_3CO_2H$: C, 75.07; H, 5.35; N, 8.26. Found: C, 74.84; H, 5.40; N, 8.22.

3,4,6,7-Tetrahydro-4,6-dithioxo-1,9-di(3,3,3-triphenylpropyl)pyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,8(1*H*,9*H*)-dione (12). To a mixture of 100 mg (0.13 mmol) of **11** in 5 mL of pyridine was added, with stirring, 230 mg (1.0 mmol) of phosphorus pentasulfide. The mixture was heated to reflux for 19 h. The solution was cooled and the pyridine was evaporated to about one-third of the initial volume. The residue was poured into 10 mL of water and the solid formed was filtered, washed with 1:2 (v/v) pyridine–water, and dried to give 90 mg (83%) of **12** as a yellow powder: mp 178–180 °C; ^{1}H NMR (DMSO-d_6): δ 13.13 (2H, s, 2NH), 9.40 (1H, s, ArH), 7.17–7.11 (30H, m, $2CPh_3$), 3.92 (4H, br, $2CH_2$), 2.80 (4H, br, $2CH_2$); HRMS calcd for $C_{51}H_{41}N_5O_2S_2$: 819.2702; found: 819.2706.

4,6-Diamino-1,9-di(3,3,3-triphenylpropyl)pyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,8(1*H*,9*H*)-dione (1). A mixture of 70 mg (0.085 mmol) of **12** in 5 mL of methanol, saturated with gaseous ammonia at 0 °C, was heated to 100 °C in a sealed tube. Within 10 min a white precipitate formed and the solution turned green. After heating for 20 h the mixture was cooled to room temperature, filtered, and the solid washed with methanol and thoroughly dried to give 65 mg (97%) of **1** as a white powder: mp 265–267 °C; ^{1}H NMR (DMSO-d_6): δ 8.97 (1H, s, ArH), 8.1 (4H, br, $2NH_2$), 7.11 (30H, m, $2CPh_3$), 4.01 (4H, m, $2CH_2$), 2.75 (4H, m, $2CH_2$). FABMS (MH^+) 786; HRMS calcd for $C_{51}H_{44}N_7O_2$: 786.3556; found: 786.3558. X-ray analysis: see text.

Dimethyl (±)-1-(2-ethylhexyl)-2,5-dimethylpyrrole-3,4-dicarboxylate (14). To a mixture of 1.00 g (4.35 mmol) of **13** and 2.00 g (15.5 mmol) of (±)-2-ethylhexylamine was added 0.5 mL of acetic acid. The resulting mixture was stirred at room temperature for 24 h, and poured into an aqueous saturated solution of sodium bicarbonate. The mixture extracted with methylene chloride. The organic layer was dried over sodium sulfate, and the solvent removed under reduced pressure to give a brown oil. Flash chromatography (6% ethyl acetate–methylene chloride) afforded 1.36 g (97%) of **14** as a colorless oil: ^{1}H NMR δ 3.80 (s, 6H, OMe), 3.66–3.63 (m, 2H, NCH_2), 2.36 (s, 6H, CH_3), 1.72–1.60 (m, 1H, CH), 1.38–1.15 (m, 8H, CH_2), 0.91–0.86 (m, 6H, CH_3); ^{13}C NMR: δ 166.2, 133.7, 112.1, 51.3, 48.0, 40.2, 30.5, 28.7, 23.8, 23.0, 14.0, 11.4, 10.9; MS (EI, 70 eV): *m*/*z* (relative intensity) 323 (M^+, 43), 276 (100); HRMS calcd for $C_{18}H_{29}NO_4$: 323.2097; found 323.2105. Anal. calcd for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04; N, 4.33. Found: C, 66.68; H, 9.20; N, 4.75.

Dimethyl (±)-1-(2-ethylhexyl)-2,5-bis(bromomethyl)-pyrrole-3,4-dicarboxylate (15). A mixture of 256 mg (0.79 mmol) of **14**, 358 mg (2.0 mmol) of *N*-bromosuccinimide, and 50 mL of carbon tetrachloride was irradiated by a 100 watt light bulb for 25 min, which also heated the solution to reflux. The mixture was filtered and solvent removed under reduced pressure to give an oil. Flash chromatography (4% ethyl acetate–methylene chloride) afforded 340 mg (89%) of **15** as a yellow oil: ^{1}H NMR: δ 4.73 (d, $J = 2.8$, 4H, CH_2Br), 4.01–3.97 (m, 2H, NCH_2), 3.86 (s, 6H, OMe), 1.90–1.79 (m, 1H, CH), 1.42–1.18 (m, 8H, CH_2), 0.97–0.89 (m, 6H, CH_3); ^{13}C NMR: δ 164.4, 133.5, 115.7, 52.0, 48.7, 40.7, 30.7, 28.7, 24.0, 22.9, 20.9, 14.0, 10.9; MS (EI, 70 eV): *m*/*z* (relative intensity) 481 (M^+, 2), 479 (M^+, 1), 41 (100); HRMS calcd for $C_{18}H_{27}Br_2NO_4$: 479.0307; found 479.0309. Anal. calcd for $C_{18}H_{27}Br_2NO_4$: C, 45.09; H, 5.68; N, 2.92; Br, 32.95. Found: C, 44.78; H, 5.69; N, 2.88; Br, 33.39.

Dimethyl (±)-1-(2-ethylhexyl)-2,5-bis(acetonitrile)pyrrole-3,4-dicarboxylate (16). A solution of 500 mg (3.21 mmol) of tetraethylammonium cyanide in 15.0 mL of methylene chloride was added to a solution of 270 mg (0.56 mmol) of **15** in 25.0 mL of methylene chloride via a cannula. The resulting mixture was stirred at room temperature for 24 h. Removal of the solvent under reduced pressure gave a brown residue. Flash chromatography (4% v/v ethyl acetate:methylene chloride) afforded 150 mg (72%) of **16** as a yellow oil: ^{1}H NMR: δ 4.03 (d, $J = 2.3$, 4H, CH_2CN), 3.96–3.93 (m, 2H, NCH_2), 3.86 (s, 6H, OCH_3), 1.80–1.68 (m, 1H, CH), 1.43–1.11 (m, 8H, CH_2), 0.97–0.87 (m, 6H, CH_3); ^{13}C NMR: δ 164.2, 126.5, 115.5, 115.1, 52.1, 49.2, 40.8, 30.6, 28.6, 23.8, 22.9, 14.5, 13.9, 10.8; MS (EI, 70 eV): *m/z* (relative intensity) 373 (M^+, 5), 301 (100); HRMS calcd for $C_{20}H_{27}N_3O_4$: 373.2002; found 373.2004.

(±)-9-(2-Ethylhexyl)-2,7-diamino-3,4,5,6-tetrahydro-3,6-diazafluorene-4,5-dione (2). To a sealed tube containing a solution of 300 mg (0.80 mmol) of **16** in 0.5 mL of methanol was added 4 mL of 30% aqueous ammonium hydroxide and the resulting mixture was heated at 100–110 °C. The mixture turned homogeneous after 0.5 h and precipitate started to form after 4–5 h. Heating was continued for a total of 40 h. The precipitate was filtered upon cooling, washed excessively with water, and dried to afforded 60 mg (22%) of **2** as an off-white solid: mp >250 °C, dec; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.85 (br s, 2H, NH), 5.67 (s, 2H, H-1, H-8), 5.67 (br s, 4H, NH_2), 3.73 (d, $J = 7.4$, 2H, NCH_2), 1.78–1.76 (m, 1H, CH), 1.29–1.20 (m, 8H, CH_2), 0.87–0.79 (m, 6H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): d 156.9 (br), 148.5, 97.7, 76.5 (br), 47.3, 38.6, 30.3, 28.2, 23.7, 22.7, 14.0, 10.8 (1 carbon missing); MS (EI, 70 eV): *m/z* (relative intensity) 343 (M^+, 16), 66 (100); HRMS calcd for $C_{18}H_{25}N_5O_2$: 343.2087; found 343.2091.

Acknowledgements

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20. Crystal data for **1**: monoclinic; space group *I*2/*a*; $a = 17.760(6)$, $b = 20.120(3)$, $c = 19.947(3)$ Å, $\beta = 111.90(2)°$; $V = 6613(3)$ Å^3, $Z = 4$, $D_c = 1.227$ mg m^{-3}; data were measured at 198 K on an Enraf–Nonius CAD4 diffractometer with final $R = 0.0517$ for 5810 reflections. For questions about the X-ray analysis, contact Scott R. Wilson, Department of Chemistry, University of Illinois, Urbana, IL 61801, U.S.A.

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