Synthesis of a Novel Pyrrolo[2,3-*d*]pyrimidine Alkaloid, Rigidin

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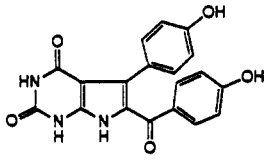
An efficient nine-step synthesis of the brain phosphodiesterase inhibitor, rigidin, has been accomplished in 26% overall yield starting from 6-chlorouracil and ethyl (2,4-dimethoxybenzyl)glycinate. A key feature of the synthetic route reveals a new method for the annulation of pyrrole rings onto pyrimidine rings starting from 6-chlorouracils and *N*-benzylglycine sodium salts. Thus, initial condensation adducts **7a,b** were converted into 5-acetoxypyrroles **8a,b** upon warming in acetic anhydride. The readily derived 5-(trifluoromethanesulfonyl)oxy materials **8c,f** undergo palladium-catalyzed cross couplings with aryltin reagent **9** and afford C-5 aryl compounds **10a,b**. Acylation at the C-6 position in **10a,b** was best effected using a mixed anhydride reagent derived from acid **11** and TFAA. The optimal route to ridigin (**1d**) involved a one-pot deprotection procedure of intermediate **1b** using excess TMSI followed by heating in water.

A novel pyrrolo[2,3-*d*]pyrimidine alkaloid, rigidin (**1**), was recently isolated from the Okinawan marine tunicate *Eudistoma* cf. *rigida*.[1] Of some signficance was that this compound was found to inhibit calmodulin-activated brain phosphodiesterase with an I_{50} value of 5×10^{-5}M. However, it is not clear how rigidin functions biologically. A major question is whether this compound binds to the calcium/calmodulin complex or inhibits by directly acting on the enzyme which is activated by the complex. The discovery of new pharmacological agents which inhibit specific calmodulin-sensitive enzymes could serve as valuable research tools.[2] Unfortunately, the limited availability of this material (0.0015% wet weight) from localized tunicate species makes further biological testing unfeasible. In this way, total synthesis can play an important role by providing quantities of synthetic material as revealed in the following discussion.



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The presence of highly substituted pyrrole rings fused to six-membered rings is an important structural subunit in a variety of biologically active compounds. In particular, the presence of pyrrolo[2,3-*d*]pyrimidines ring systems in naturally occurring antibacterial/antitumor compounds[3] and various bioactive nucleotide analogs[4] warrants the development of new, more efficient, synthetic methodologies. The available methods[5] for the construction of these compounds are often limited due to lengthy reaction sequences,[3d,e] low-yielding steps,[5c,d,g] or a lack of functionality,[5d,e,h] especially at the C-5 position, in the parent ring system.

We were intrigued by the opportunity to quickly access rigidin using new methodology being developed in our laboratory for the synthesis of pyrrolo[2,3-*d*]pyrimidine and indole ring systems (Scheme I). In a way related to Frank's approach[6] to the mitomycin skeleton, the combination of amino acid salts with either β-chloro enones or 1,3-dicarbonyl compounds affords substitution products **2**. These materials are internally cyclized to 3-acetoxypyrrole derivatives **3** upon exposure to acetic anhydride. We have found that further conversion of **3** into the trifluoromethyl sulfonate derivatives **4** generates substrates which undergo facile palladium-catalyzed cross-coupling reactions[7] with a variety of organotin reagents. The resulting 3-substituted pyrrole adducts **5** can then serve as versatile synthetic intermediates. The advantages of this approach include the use of readily available and inexpensive starting materials and reagents, an efficient and overall high yielding reaction sequence, and the ability to introduce a wide variety of functional groups at the C-5 position using mild palladium-catalyzed cross-coupling chemistry.

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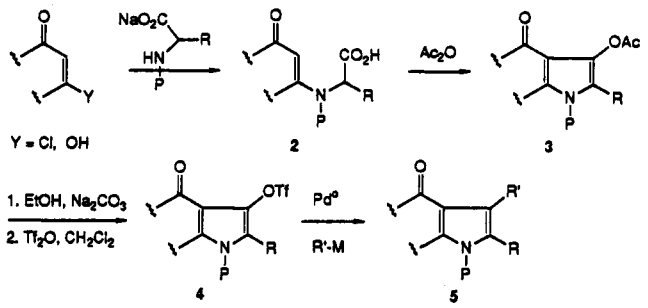
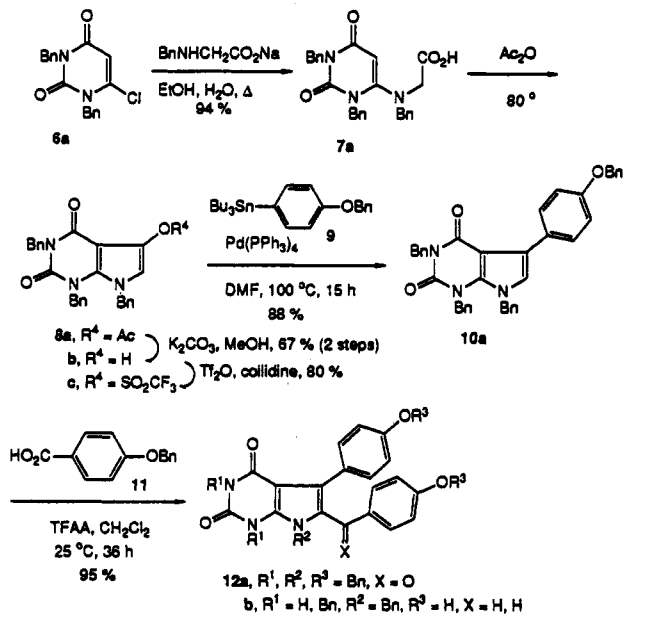
Scheme I



Scheme II



Our initial effort focused on the preparation of pentabenzyl rigidin, **12a**, as shown in Scheme II. The choice of benzyl protecting groups was largely a consequence of providing stable and easily identifiable intermediates which would allow us to focus the development of an efficient reaction sequence leading to the skeleton of **1**. Thus, combination of 6-chloro-1,3-dibenzyluracil[8] with the sodium of *N*-benzylglycine afforded the substitution adduct **7a** in high yield following an acidic workup. Ring closure of **7a**, via an internal acylation reaction, was conveniently promoted by heating in acetic anhydride at 80 °C for 4 h. The resulting 3-acetoxypyrrole was hydrolyzed to the 5-hydroxy derivative **8b** in 65% yield for the two steps. Conversion of **8b** into the triflate **8c** occurred without incident.[9] The palladium-catalyzed cross coupling with the electron-rich arylstannane **9** using typical Stille conditions[4] afforded cross-coupled adduct **10a** in high yield. Acylation of **10a** was carried out most efficiently using a preformed mixed anhydride reagent[10] derived from 4-(benzyloxy)benzoic acid (**11**) and TFAA. The reaction of this reagent with the activated pyrrole ring in **10a** was found to proceed more readily upon the addition of 6.0 equiv of TFA to the reaction mixture and stirring at room temperature for 16 h. The pentabenzylrigidin precursor **12a** was then isolated in 95% yield.

The optimism resulting from the easy preparation of the precursor **12a** was quickly diminished following numerous attempts to remove its five benzyl protecting groups and provide rigidin. Under typical hydrogenation conditions, a single product was obtained in high yield whose spectral data was consistent with the structure shown in **12b**. ^{1}H NMR confirmed the presence of two remaining benzyl groups, presumably on the pyrrole nitrogen and one of the pyrimidine nitrogens. The appearance of a new singlet at 3.65 ppm and the lack of a conjugated C=O stretch in the IR clearly suggested that the C-14 carbonyl group had been reduced to a methylene. Other reported debenylation procedures using acidic reagents were also tried with little success (BBr_3,[11a] HBr/AcOH, TMSI/CH_3CN[11b]). Dissolving sodium conditions[12a] or sodium naphthalide[12b] afforded only low yield of the natural material accompanied with several side products.

In considering a new protection strategy, it was felt that acid-labile groups such as (benzyloxy)methyl (BOM)[13a] for the uracil type nitrogens and an electron-rich benzyl group[13b] at the pyrrole nitrogen would provide the most flexible and efficient deprotection scheme. The appropriate choice of either protic or Lewis acidic reagents for the final deprotection step could be determined and thereby avoid destruction of the C-14 carbonyl functionality.

Starting with 6-chlorouracil (**6b**), alkylation with BOMCl using lithium hydride as a base afforded 86% of 6-chloro-1,3-bis((benzyloxy)methyl)uracil (**6c**). The readily obtained *N*-(2,4-dimethoxybenzyl) derivative of sodium glycinate[14] was condensed with **6c** in refluxing ethanol to provide the substitution product **7b**. Warming of **7b** in acetic anhydride followed by a brief reflux provided the 3-acetoxypyrrolo[2,3-*d*]pyrimidine **8d** in 76% yield over two steps. Subsequent acetate hydrolysis and then immediate processing of the hydroxypyrrole led to the crystalline triflate derivative **8f** (85%, two steps). Cross coupling of **8f** using stannane **9** and under typical Stille conditions proceeded poorly (23% of **10b**) in contrast to the benzyl derivative **8c**. Fortunately, the procedure recently developed by Farina et al.[15] using the air stable Pd^0 source of $Pd_2(dba)_3$ and trifurylphosphine as the ligand provided a satisfactory 76% yield of the C-5 aryl adduct **10b**. The acylation at the C-6 position of **10b** proved to be one of the more challenging steps to optimize. Prior mixing of carboxylic acid **10b** with TFAA followed by stirring with **10b** for 36 h at 25 °C afforded an 18% yield of the fully protected rigidin precursor **1a** and 47.4% of

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(9) The conditions using 2,4,6-collidine/Tf_2O and having the reaction warm from −78 to 25 °C were chosen mainly to avoid using more expensive reagents such as 2,6-di-*tert*-butyl-4-methylpyridine or *N*-phenyltriflimide. Stang, P. J.; Hanack, M. C.; Subramanian, L. R. *Synthesis* **1982**, 85. McMurray, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

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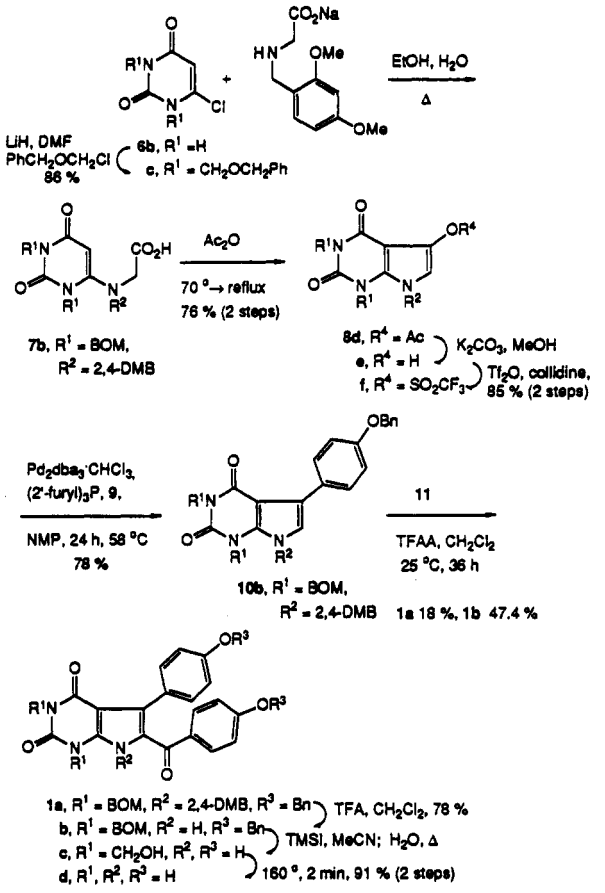
(13) (a) Kundu, N. G.; Khatri, S. G. *Synthesis* **1985**, 323. Kundu, N. G. *Synth. Commun.* **1981**, *11*, 787. (b) A 2,4-dimethoxybenzyl group was first used to protect a secondary amide and was readily cleaved using TFA at room temperature. Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. Y. *J. Am. Chem. Soc.* **1985**, *107*, 1777.

(14) See the Experimental Section. The ethyl *N*-(2,4-dimethoxybenzyl)gycinate was prepared by the reaction of 2,4-dimethoxybenzylamine with ethyl bromoacetate in refluxing benzene. The material was purified by simple distillation.

(15) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C., Jr. *J. Org. Chem.* **1990**, *55*, 5833.

Scheme III



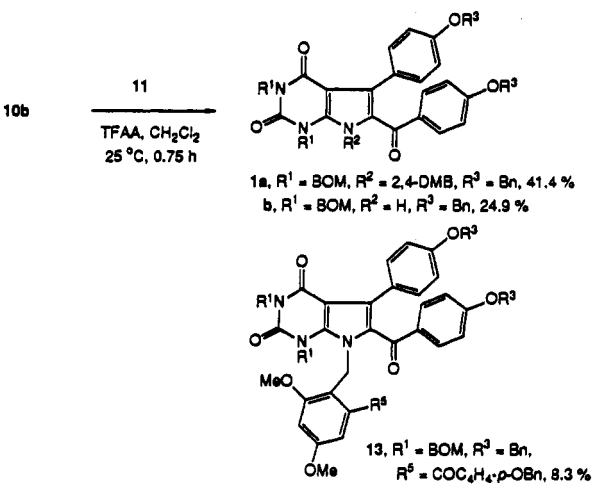
1b, which resulted from further cleavage of the dimethoxybenyl group under the acidic reaction conditions. This later material was found to be most efficiently converted into the natural product using the following protocol: cleavage of the remaining benzyloxy and benzyl group using excess TMSI in refluxing acetonitrile followed by heating of the crude 1,3-bis(iodomethyl) intermediate in water to provide the readily isolated bis(hydroxymethyl) compound **1c**.[13a] Simple heating of **1c** at 160 °C for 2 min afforded a pure sample of rigidin[16] in 91% overall yield for the complete deprotection procedure. The pyrrole-protected acylation product **1a** could be conveniently converted into **1b** by treatment with TFA in CH_2Cl_2. Attempts to convert **1a** directly into **1d** using the above protocol proceeded in somewhat lower yields and was complicated by the appearance of minor byproducts.

The reaction conditions controlling the key acylation step were explored in greater detail (Scheme IV). It was found that exposure of **10b** to the mixed anhydride reagent for short reaction times (30–45 min) afforded a mixture of **1a** (41.4%), **1b** (25%), and a higher molecular weight material, **13** (8.3%), resulting from further acylation at the electron-rich dimethoxybenzyl group. Running the reaction with 1 equiv of reagent (vs 1.25 equiv) minimized the appearance of **13** but also led to a lower conversion of **10b** into either **1a** or **1b**.

In conclusion, we have provided the first total synthesis of rigidin (**1d**) in nine steps and nearly 26% overall yield starting from 6-chlorouracil and ethy(2,4-dimethoxybenzyl)glycinate. Our methodology should reveal considerable potential for the synthesis of a wide variety of pyrrole-annulated heterocycles. Applications directed toward the synthesis of specific pyrrolo[2,3-*d*]pyrimidines, 3,4-disubstituted indoles, and indoloquinones are currently being pursued.

(16) The color of our synthetic material was a deep yellow, λ_{max} (ϵ) 356 (14 110). The reported color of naturally isolated rigidin was described as "purple" and revealed an extra absorption at λ_{max} of 401 (2500) (ref 1). We believe this to be ascribable to a colored impurity coisolated from the marine tunicate.

Scheme IV



Experimental Section

The following solvents and reagents were distilled from calcium hydride under a nitrogen atmosphere: dichloromethane, 2,4,6-collidine, 1-methyl-2-pyrrolidinone (NMP), acetonitrile, and chlorotrimethylsilane. DMF (0.034% of water) was purchased from EM Industries, Inc., and used without further purification. Melting points were recorded on a Thomas-Hoover apparatus and are uncorrected. IR spectra were determined with an FTIR instrument. ^1H NMR spectra were recorded at 270 or 300 MHz with tetramethylsilane or DMSO (δ 2.49) used as the internal references. ^{13}C NMR were recorded at 67.9 MHz; $CDCl_3$ (δ 77.0) or DMSO (δ 39.5) were used as the internal references. Elemental analyses were performed by Atlantic Microlab, Inc. Column chromatography was performed with silica gel (Merck 60 Å, 230–400 mesh). The final product solutions were dried over Na_2SO_4 and concentrated on a rotary evaporator.

6-Chloro-1,3-bis((benzyloxy)methyl)uracil (6c). A solution of 6-chlorouracil (4.00 g, 27.2 mmol) in DMF (100 mL) under an atmosphere of dry N_2 was cooled to 0 °C and treated with LiH (0.54 g, 68.0 mmol). After the mixture was stirred for 30 min, (benzyloxy)methyl chloride (9.34 g, 59.8 mmol) was added slowly to the mixture over a period of 30 min. The mixture was allowed to warm to room temperature and was stirred for 5 h. The progress of the reaction was monitored by TLC (EtOAc) until the 6-chlorouracil had been consumed and the monoalkylated uracil had disappeared. The reaction mixture was then poured onto ice–water (200 mL), and the resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with water (3 × 100 mL) and brine (100 mL), dried, and then concentrated. The residue was crystallized from ethyl acetate/hexanes to afford 8.15 g of **6c** as a white powder. Flash chromatography of the recrystallization mother liquor using hexanes/ethyl acetate (1.5:1.0) provided an additional 0.85 g of **6c** (total yield 85.5%). An analytical sample of **6c** was obtained by recrystallization from ethanol/water as colorless needles: mp 97–98 °C; IR (KBr) 3065–2874, 1719, 1670, 1615, 1112, 1073 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 7.39–7.25 (10 H, m), 5.88 (1 H, s), 5.55 (2 H, s), 5.41 (2 H, s), 4.69 (2 H, s), 4.67 (2 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 160.3, 151.2, 145.9, 137.7, 137.0, 128.4, 128.2, 128.0, 127.7, 127.5, 103.1, 75.2, 72.3, 72.1, 70.9.

Anal. Calcd for $C_{20}H_{19}ClN_2O_4$: C, 62.10; H, 4.95; N, 7.24. Found: C, 62.00; H, 4.96; N, 7.27.

1,3-Bis((benzyloxy)methyl)-6-[*N*-(2,4-dimethoxybenzyl)-*N*-(carboxymethyl)amino]uracil (7b). A mixture of NaOH (0.620 g, 15.5 mmol) and *N*-(2,4-dimethoxybenzyl)glycine ethyl ester (3.92 g, 15.5 mmol) in 20 mL of water were refluxed for 1

h. After 13 mL of water was distilled off, **6c** (2.00 g, 5.1 mmol) and 18 mL of ethanol were added to the reaction mixture. The mixture was refluxed for 1.5 h, and Na_2CO_3 (0.53 g, 5 mmol) was added. The resulting mixture was refluxed for 13.5 h and then was concentrated under reduced pressure. The residue was dissolved in 100 mL of water, acidified with concentrated HCl to pH 2–3, and then extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL) and dried. The solution was filtered and concentrated to give 5.80 g of crude **7b** as a light yellow glass (this material was used in the next step without further purification): IR (KBr) 3384 (br), 2937, 1708, 1615, 1508, 1455, 1209, 1089, 1074 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.06 (11 H, m), 6.44–6.41 (2 H, m), 5.45 (2 H, s), 5.41 (2 H, s), 5.35 (1 H, s), 4.75 (2 H, s), 4.71 (2 H, s), 4.31 (2 H, s), 3.86 (2 H, s), 3.79 (3 H, s), 3.72 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 172.3, 163.6, 161.1, 159.4, 158.7, 153.3, 137.9, 137.4, 131.1, 128.4, 128.2, 127.8, 127.6, 115.1, 104.2, 98.6, 90.7, 75.8, 72.8, 72.5, 72.1, 70.1, 70.6, 55.3, 55.1, 51.8, 51.6.

5-Acetoxy-1,3-bis((benzyloxy)methyl)-7-(2,4-dimethoxybenzyl)-2,4-dioxopyrrolo[2,3-*d*]pyrimidine (8d). A mixture of crude **7b** (5.80 g, prepared as described above) and 70 mL of Ac_2O under an atmosphere of dry N_2 was stirred for 2 h at 70 °C. The mixture was then heated to reflux for 45 min. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. Flash chromatography using hexanes/ethyl acetate (1:3) afforded 4.76 g of **8d** (76.7% for two steps) as a light yellow powder. An analytical sample was obtained by recrystallization from methanol as colorless needles: mp 127.5–128.5 °C; IR (KBr) 3063–2840, 1769, 1712, 1662, 1546, 1211, 1166, 1107, 1097, 1038, 1028 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 280 (7390), 226 (26 070, shoulder to 206), 206 (57 270); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.22 (10 H, m), 6.63 (1 H, d, J = 8.4 Hz), 6.64–6.47 (2 H, m), 6.41 (1 H, dd, J = 2.0, 8.4 Hz), 5.53 (2 H, s), 5.53 (2 H, br s), 5.34 (2 H, br s), 4.72 (4 H, s), 3.80 (3 H, s), 3.79 (3 H, s), 2.34 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 168.8, 161.0, 157.2, 157.1, 152.3, 138.1, 137.2, 134.5, 132.7, 128.3, 128.2, 127.8, 127.6, 127.5, 127.4, 117.2, 112.2, 104.4, 98.8, 73.3, 72.0, 71.6, 70.7, 55.4, 55.3, 47.4, 20.7.

Anal. Calcd for $C_{13}H_{33}N_3O_8$: C, 66.10; H, 5.55; N, 7.01. Found: C, 65.86; H, 5.58; N, 6.95.

1,3-Bis((benzyloxy)methyl)-7-(2,4-dimethoxybenzyl)-2,4-dioxo-5-hydroxypyrrolo[2,3-*d*]pyrimidine (8e). A mixture of finely powdered **8d** (1.95 g, 3.1 mmol) and $Na_2CO_3 \cdot H_2O$ (5.00 g, 40 mmol) in 100 mL of methanol was stirred vigorously and rapidly heated to reflux using a 90 °C oil bath in the period of 3–5 min. The reaction mixture was cooled with an ice–water bath to room temperature. The excess sodium carbonate solid was removed by filtration, and the filtrate was treated with 100 mL of cooled water and extracted with CH_2Cl_2 (2 × 70 mL). The combined organic layers were washed with 2% HCl (70 mL) and brine (100 mL), dried, filtered, and concentrated. Flash chromatography of the residue using ethyl acetate provided 1.54 g (84.6%) of **8e** as light yellow solid: mp 151–152 °C; IR (KBr) 3041–2837 (CH), 1737, 1693, 1640, 1581, 1512, 1455, 1294, 1208, 1114, 1093, 1028 cm-1; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43–7.25 (10 H, m), 6.93 (1 H, d, J = 7.6 Hz), 6.48–6.44 (2 H, m), 5.56 (2 H, br s), 5.47 (2 H, s), 4.98 (2 H, br s), 4.80 (2 H, s), 4.71 (2 H, s), 3.87 (2 H, s), 3.81 (3 H, s), 3.78 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 187.6, 165.1, 161.5, 158.0, 155.8, 152.0, 138.0, 136.7, 128.7, 128.4, 128.2, 128.1, 127.7, 127.6, 127.5, 115.1, 104.5, 99.0, 93.6, 73.5, 72.5, 72.0, 70.1, 60.8, 55.4, 55.3, 48.2.

1,3-Bis((benzyloxy)methyl)-7-(2,4-dimethoxybenzyl)-2,4-dioxo-5-((trifluoromethanesulfonyl)oxy)pyrrolo[2,3-*d*]pyrimidine (8f). A mixture of **8e** (1.44 g, 2.59 mmol) and 2,4,6-collidine (0.447 g, 3.69 mmol) in 10 mL of CH_2Cl_2 at −78 °C was treated with triflic anhydride (1.04 g, 3.69 mmol). The mixture was stirred at −78 °C for 15 min and diluted with CH_2Cl_2 (50 mL). The solution was washed with brine (50 mL), dried, and concentrated. Flash chromatography using hexanes/ethyl acetate (1.0:1.9) afforded 1.78 g (99%) of **8f** as a pale orange oil: IR (thin film) 3156–2840, 1717, 1682, 1616, 1550, 1456, 1288, 1209, 1141, 1076 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.22 (10 H, m), 6.65 (1 H, d, J = 8.3 Hz), 6.47–6.42 (3 H, m), 5.54 (2 H, s), 5.49 (2 H, br s), 5.37 (2 H, br s), 4.73 (2 H, s), 4.72 (2 H, s), 3.81 (3 H, s), 3.80 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 161.4, 157.5, 156.4, 151.9, 138.1, 137.0, 134.8, 130.5, 128.4, 128.0, 128.0, 127.5, 121.1, 118.2, 116.2, 113.2, 104.6, 98.9, 73.4, 72.1, 72.0, 70.8, 55.4, 55.4, 48.1.

5-(4-(Benzyloxy)phenyl)-1,3-bis((benzyloxy)methyl)-7-(2,4-dimethoxybenzyl)-2,4-dioxopyrrolo[2,3-*d*]pyrimidine (10b). A solution of **8f** (0.94 g, 1.36 mmol) in 5 mL of NMP was degassed with nitrogen. Zinc chloride (0.37 g, 2.72 mmol) and tri(2-furyl)phosphine (30 mg, 0.129 mmol) were then added. The mixture was stirred at room temperature for 5 min, and Pd_2dba_3 (29 mg, 0.06 mmol) was added to the mixture. The mixture was stirred for 10 min, and then (*p*-(benzyloxy)phenyl)tri-*n*-butyltin (0.97 g, 1.36 mmol) was added. The reaction mixture was stirred at 55 °C for 24 h, diluted with ethyl acetate (100 mL), washed with water (3 × 50 mL) and brine (50 mL), and dried. Concentration of the organic phase gave a residue which was redissolved in acetonitrile (100 mL) and washed with pentane (2 × 100 mL). Evaporation of the polar phase and flash chromatography of the residue using hexanes/ethyl acetate (1.9:1.0) afforded 0.75 g (76.2%) of **10b** as a white solid. An analytical sample was obtained by recrystallization from hexanes/ethyl acetate as a white solid: mp 131–132 °C; IR (KBr) 3031–2935, 1707, 1663, 1618, 1552, 1523, 1455, 1212 cm^{-1}; UV ($CHCl_3$) λ_{max} (ϵ) 298 (12 750, shoulder to 284), 284 (14 190, shoulder to 242), 242 (35 680); ^1H NMR ($CDCl_3$, 270 MHz) δ 7.58 (2 H, d, J = 8.6 Hz), 7.56–7.20 (15 H, m), 6.99 (2 H, d, J = 8.6 Hz), 6.58 (1 H, d, J 8.6 Hz), 6.48–6.37 (3 H, m), 5.58 (2 H, s), 5.48 (2 H, br s), 5.42 (2 H, br s), 5.08 (2 H, s), 4.73 (4 H, s), 3.81 (3 H, s), 3.78 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 160.9, 158.4, 157.0, 152.3, 138.3, 137.6, 137.3, 137.2, 130.0, 128.5, 128.3, 128.2, 127.8, 127.8, 127.5, 127.4, 127.4, 127.3, 125.7, 122.7, 120.7, 117.6, 114.4, 104.4, 98.8, 73.3, 72.1, 71.7, 71.1, 70.0, 55.4, 47.4.

Anal. Calcd for $C_{44}H_{41}N_3O_7$: C, 73.01; H, 5.71; N, 5.81. Found: C, 73.03; H, 5.71; N, 5.83.

6-(4-(Benzyloxy)benzoyl)-5-(4-(benzyloxy)phenyl)-1,3-bis((benzyloxy)methyl)-7-(2,4-dimethoxybenzyl)-2,4-dioxopyrrolo[2,3-*d*]pyrimidine (1a) and 6-(4-(Benzyloxy)benzoyl)-5-(4-(benzyloxy)phenyl)-1,3-bis((benzyloxy)methyl)-2,4-dioxopyrrolo[2,3-*d*]pyrimidine (1b). A mixture of *p*-(benzoyloxy)benzoic acid (158 mg, 0.693 mmol) and trifluoroacetic anhydride (145 mg, 0.693 mmol) in 2.5 mL of CH_2Cl_2 was stirred at room temperature for 10 min. Trifluoroacetic acid (378 mg, 3.315 mmol) and **10b** (400 mg, 0.552 mmol) were then added. The resulting solution was stirred for 36 h at room temperature, diluted with CH_2Cl_2 (50 mL), washed with 5% Na_2CO_3 (50 mL), and dried. Evaporation and flash chromatography of the residue using hexanes/ethyl acetate (1.9:1.0) afforded 206 mg (47.5%) of **1b** as a light yellow solid and 89 mg (18%) of **1a** as a pink foam. An analytical sample of **1b** was obtained by recrystallization from hexanes/ethyl acetate as an off-white solid: mp 176–178.5 °C; IR (KBr) 3234, 1716, 1678, 1601, 1543, 1250, 1173; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.22 (22 H, m), 7.10 (2 H, d, J = 8.5 Hz), 6.71 (2 H, d, J = 8.0 Hz), 6.61 (2 H, d, J = 8.1 Hz), 5.64 (2 H, s), 5.53 (2 H, s), 4.99 (4 H, s), 4.70 (2 H, s), 4.68 (2 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 186.3, 161.7, 158.6, 158.4, 151.0, 139.8, 138.1, 136.8, 136.5, 161.1, 132.5, 131.6, 130.9, 129.6, 128.5, 128.4, 128.2, 128.1, 113.8, 113.7, 99.9, 73.4, 72.1, 71.8, 70.8, 70.0, 69.9.

Anal. Calcd for $C_{49}H_{41}N_3O_7$: C, 75.08; H, 5.27; N, 5.36. Found: C, 74.84; H, 5.39; N, 5.21.

For **1a**: IR (thin film) 3063–2937, 1714, 1673, 1598, 1525, 1508, 1292, 1251 cm^{-1}; UV ($CHCl_3$) λ_{max} (ϵ) 338 (11 330, shoulder to 282), 282 (35 650), 242 (41 760); ^1H NMR ($CDCl_3$, 270 MHz) δ 7.45–7.23 (22 H, m), 7.15 (2 H, d, J = 8.6 Hz), 6.70 (2 H, d, J = 8.6 Hz), 6.62 (2 H, d, J = 9.2 Hz), 6.53 (1 H, d, J = 8.6 Hz), 6.38 (1 H, d, J = 2.0 Hz), 6.30 (1 H, dd, J = 2.0, 8.2 Hz), 5.73 (2 H, s), 5.55 (2 H, s), 5.50 (2 H, br s), 4.97 (2 H, s), 4.94 (2 H, s), 4.76 (2 H, s), 4.72 (2 H, s), 3.74 (3 H, s), 3.71 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 187.1, 162.2, 160.4, 158.2, 156.7, 152.5, 140.8, 138.2, 137.3, 137.0, 136.8, 132.1, 132.1, 130.9, 128.6, 128.5, 128.3, 128.2, 128.1, 127.8, 127.5, 127.5, 127.4, 127.3, 126.8, 124.1, 118.7, 113.8, 113.7, 104.1, 98.6, 74.0, 72.2, 71.1, 70.0, 69.8, 55.3, 55.3, 45.2.

1b from 1a. The mixture of **1a** (70 mg, 0.076 mmol) and 0.26 mL of trifluoroacetic acid in 1.5 mL of dry CH_2Cl_2 was stirred at room temperature for 36 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with 5% Na_2CO_3 (20 mL), and

dried. Evaporation and flash chromatography of the residue using hexanes/ethyl acetate (1.9:1.0) provided 46 mg (77.4%) of **1b**.

Rigidin (1d). A mixture of **1b** (150 mg, 0.191 mmol) and NaI (430 mg, 2.867 mmol) in 2 mL of CH_3CN under nitrogen was stirred at room temperature for 10 min. Chlorotrimethylsilane (311 mg, 2.867 mmol) was then added. The mixture was stirred at 57–60 °C for 16 h before the volitiles were removed in vacuo. The residue was extracted with pentane (3 × 20 mL) in order to remove benzyl iodide and then treated with 5 mL of water and 10 mL of ethyl acetate. The mixture was stirred vigorously at room temperature for 2 h and extracted with more ethyl acetate (2 × 40 mL). The combined organic layers were washed with brine (5 mL) containing a small amount of sodium thiosulfate, dried, and concentrated. The residue was mixed with 12 mL of water and boiled under N_2 to dryness using a 120 °C oil bath. A solution of 5 mL of water and several crystals of sodium thiosulfate was then added. The mixture was boiled again to dryness and heated with a 160 °C oil bath for 2 min to afford crude **1d**. ^1H NMR showed essentially clean product. Flash chromatography of the residue using ethyl acetate/methanol/acetic acid (18:1:1) afforded 63 mg (90.7%) of **1d** as a bright yellow powder: mp >300 °C; UV (MeOH) λ_{max} (ϵ) 356 (14 110), 308 (14 860, shoulder to 278), 278 (21 070), 228 (24 430, shoulder to 206), 206 (39 780); IR (KBr) 3180, 1695, 1573, 1443, 1407, 1274 cm^{-1}; ^1H NMR (DMSO, 270 MHz) δ 11.79 (1 H, br s), 11.22 (1 H, br s), 10.64 (1 H, s), 10.01 (1 H, s), 9.72 (1 H, s), 7.28 (2 H, d, J = 8.6 Hz), 6.94 (2 H, d, J = 8.6 Hz), 6.48 (2 H, d, J = 8.2 Hz), 6.44 (2 H, d, J = 8.2 Hz); ^{13}C NMR (DMSO, 67.9 MHz) δ 185.3, 160.7, 159.9, 156.5, 150.8, 141.2, 132.3, 131.6, 128.7, 128.1, 125.0, 122.8, 114.3, 113.9, 98.2. The spectral data for synthetic rigidin superimposed with the data reported for the naturally occurring material.[1]

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Supplementary Material Available: Experimental procedures for the preparation of compounds **7a**, **8a**, **8b**, **8c**, **10a**, and **12a**, including ^1H and ^{13}C NMR, IR, and mp data, and ^{13}C NMR spectra of **1d**, **7b**, **8e**, and **8f** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.