Total Synthesis of (±)-Marinopyrrole A and Its Library as Potential Antibiotic and Anticancer Agents

Chunwei Cheng,[†] Lili Pan,[†] Yi Chen,[†] Hao Song,[†] Yong Qin,[†] and Rongshi Li*[,‡]

Key Laboratory of Drug Targeting & Drug Delivery Systems of the Ministry of Education, West China School of Pharmacy, State Key Laboratory of Biotherapy, Sichuan University, Chengdu 610041, and State Key Laboratory of Bioorganic & Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 200032, P.R. China, and Department of Drug Discovery, H. Lee Moffitt Cancer Center and Research Institute, and Oncological Sciences, University of South Florida, 12902 Magnolia Drive, MRC-4072B, Tampa, Florida 33612

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The first total synthesis of marine natural product, (±)-marinopyrrole A, has been accomplished via a nine-step synthesis in an overall yield of 30%. A small focused library based on marinopyrrole has been designed and synthesized. The scope of chemistry was investigated, and a robust chemistry suitable for library synthesis has been developed in the current study. The method that we have developed has made it possible to generate diverse analogues based on structurally novel marinopyrroles for study of potential antibiotic and anticancer activities.

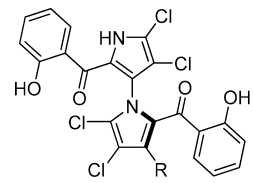
Introduction

Historically, the majority of drugs have been discovered and developed from natural products, as well as their derivatives, metabolites, and mimics. Natural-products-based drug discovery reached its peak during the 1970s and 1980s.[1] Among the small molecule new chemical entities (NCEs) introduced to the market over the past 20 years, 49%[1b] to 57.7%[1c] were natural products, synthetic or semisynthetic natural product derivatives, or compounds based on natural product "leads". Marine natural products, even though limited by technologies such as scuba diving for collecting samples, became invaluable sources of "leads" for drug discovery.[2] Because of advances in analytical technology, spectroscopy, and high-throughput screening,[3] research in the field has again become more active from both industrial and academic laboratories. The first drug from the sea, ziconotide (ω-conotoxin MVIIA) was approved by the Food and Drug Administration (FDA) in 2004 for the treatment of chronic pain in spinal cord injury.[2] Recently, the marinopyrroles A (**1a**) and B (**1b**) (Figure 1) were reported to exhibit significant antibiotic activity and cytotoxicity against a human cancer cell line (HCT-116).[4] Small samples in quantities of 15.7 mg of **1a** and 1.0 mg of **1b** were obtained by the cultivation of *Streptomyces* strain CNQ-418 in 20 L of the culture broth after purification, respectively.[4a] This unprecedented bispyrrole structure was confirmed by X-ray crystallography to adopt *M*-(−)- configuration (**1a**) which can be racemized at elevated temperature after separation to yield the non-natural *P*-(+)-atropo-enantiomer.[4a]

Combinatorial chemistry or parallel medicinal chemistry has been utilized successfully in different stages of drug discovery and development. In particular, discovery and optimization of "lead" compounds and "privileged structures" have been demonstrated in many drug discovery and development cases.[5] Modern natural products chemistry has been re-emerging to provide invaluable means for accessing and exploring the diverse structures of natural products. A combination of natural products chemistry and focused library design and synthesis is expected to be a useful and powerful tool for drug discovery and development. This structurally novel natural product inspired us to develop its chemistry and investigate the feasibility for library synthesis. In this paper, we report the first total synthesis of the racemic form of the marine natural product marinopyrrole A, and show the robustness of the method for synthesis of libraries of marinopyrrole analogues using the chemistry that we have developed.

Results and Discussion

Chemistry for Synthesis of (±)-Marinopyrroles. A nine-step synthesis of the marine natural product marinopyrrole A, (±)-**1a**, has been developed for the first time. The synthetic strategy has been established and is outlined in Scheme 1. A bis-pyrrole skeleton **4** was formed in one-pot in 82% yield via a TsOH-catalyzed condensation and cyclization reactions of 2-ethoxycarbonyl-3-aminopyrrole **2**



marinopyrrole A (**1a**), R = H
marinopyrrole B (**1b**), R = Br

Figure 1. Structure of marinopyrroles.

* To whom correspondence should be addressed. E-mail: rongshi.li@moffitt.org. Phone: (813) 745-6485. Fax: (813) 745-7264.
[†] Sichuan University and Shanghai Institute of Organic Chemistry.
[‡] Moffitt Cancer Center.

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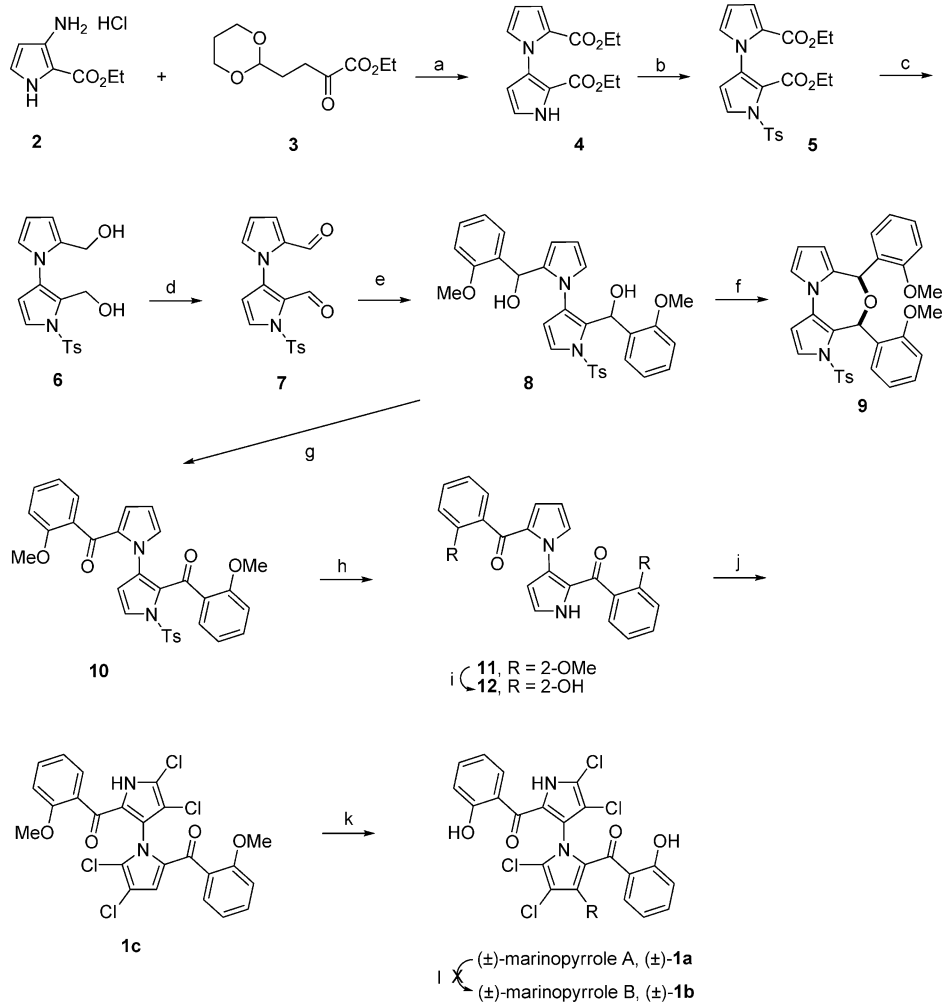
Scheme 1. Synthesis of (±)-Marinopyrrole A, Reagents and Conditions[a]



[a] (a) TsOH, toluene, reflux, 82%; (b) TsCl, DMAP, $NEt(^iPr)_2$, CH_2Cl_2, rt, 95%; (c) DIBAL-H, CH_2Cl_2, rt, 92%; (d) IBX, DMSO, 60 °C, 90%; (e) 2-MeOPhMgBr, THF, 0 °C; (f) AcOH or SiO_2, 80%; (g) CrO_3, pyridine, rt, 69% from **7**; (h) KOH, MeOH/THF (1:1), rt, 95%; (i) BBr_3, CH_2Cl_2, −78 °C, 98%; (j) NCS, MeCN, rt, 75%; (k) BBr_3, CH_2Cl_2, −78 °C, 95%; (l) NBS, MeCN. DMAP: 4-*N,N*-dimethyl pyridine; DIBAL-H: diisobutyl-aluminum hydride; IBX: 2-iodoxybenzoic acid; PCC: pyridinium chlorochromate; NCS: *N*-chlorosuccinimide; NBS: *N*-bromosuccinimide.

with α-ketone ester **3** in toluene under reflux condition.[6] After protecting the nitrogen on the pyrrole ring in **4**, the two ester groups were reduced with DIBAL-H at room temperature in CH_2Cl_2 to afford diol **6** in 87% yield in two steps. The hydroxyl groups in **6** were oxidized with IBX in dimethyl sulfoxide (DMSO) to give dialdehyde **7** in 90% yield. Although addition of 2-methoxyphenylmagnesium bromide to **7** in tetrahydrofuran (THF) or toluene at 0 °C provided diol **8** with high conversion, initial attempts to isolate the unstable **8** by chromatography on silica gel or under a weak acid condition (AcOH) exclusively afforded oxazepine **9** as byproduct with the two phenyl rings in a *cis* relationship. The relative configuration of **9** was confirmed by the X-ray analysis of a single crystal.[7] To avoid the formation of **9**, the crude **8** was directly subjected to oxidation by CrO_3 in anhydrous pyridine at room temperature to furnish diketone **10** in 69% yield and byproduct **9** in 10% yield in two steps. This operation not only supressed the byproduct formation but also saved an additional purification step. After deprotection of the Ts group in **10** in MeOH/THF (1:1), the resulting **11** was reacted with 4.4 equiv of *N*-chlorosuccinimide (NCS) in anhydrous acetonitrile to give tetrachloro-substituted **1c** in 75% yield. Demethylation of **11** was achieved using BBr_3 in CH_2Cl_2 at −78 °C to give phenol **12** in 98% yield. Compound **12** lacking the tetrachloro substituents present in **1a** was interesting for three reasons: (i) to test the importance of those tetrachloro substituents on pyrrole rings for biological activities; (ii) to explore the effects of substituents other than chlorine; (iii) to provide a site for further elaboration for Structure-Activity-Relationships (SAR). The racemic form of natural product marinopyrrole A was obtained in 95% yield in the final step by demethylation of **1c** with BBr_3. Unfortunately, attempts to prepare marinopyrrole B, (±)-**1b**, by bromination of (±)-**1a** with *N*-bromosuccinimide (NBS) under various conditions were unsuccessful. This is probably due to the electron-deficient characteristics of the pyrrole ring when it contains three electron-withdrawing groups.

Chemistry for Synthesis of a Focused Library of Marinopyrrole. Having developed a practical and robust synthetic method to racemic marinopyrrole A, analogues of marinopyrrole A shown in Figure 2 were designed and synthesized to demonstrate the suitability of the chemistry for the synthesis of libraries of marinopyrrole analogues. To investigate the scope of chemistry and feasibility that library compounds can be synthesized, we chose electron-donating,

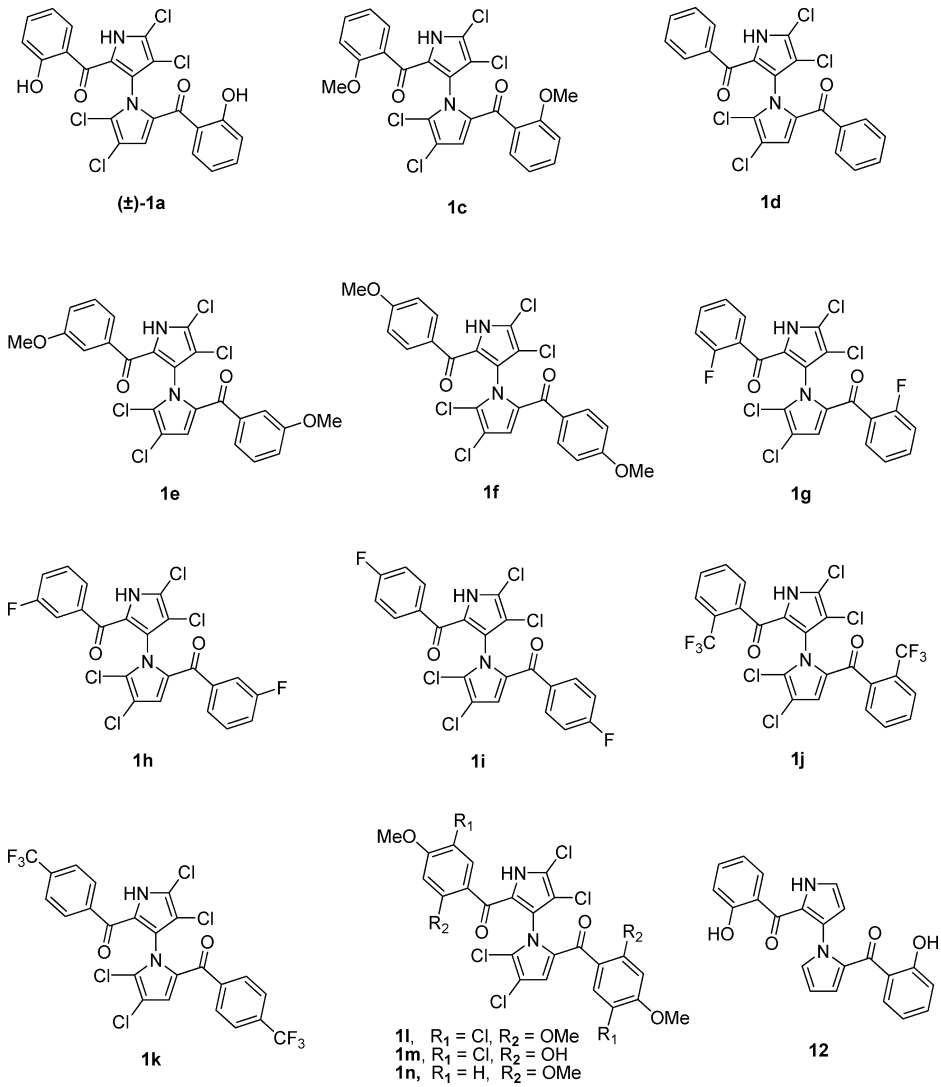
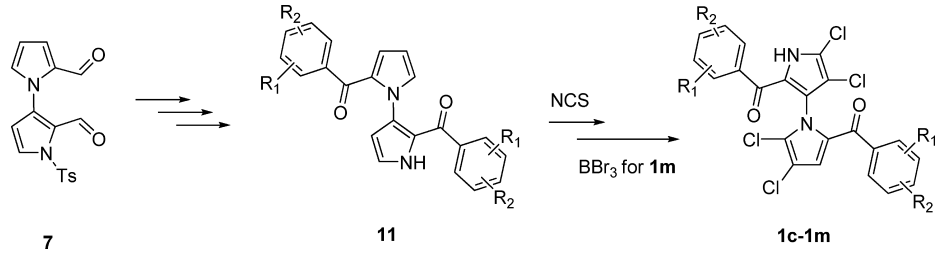


Figure 2. Focused library of marinopyrroles.

Scheme 2. Synthesis of a Focused Library of Marinopyrroles



electron-withdrawing and non-substitued phenyl rings to be installed as the phenyl-ketone moiety on bis-pyrrole system. Variation on *ortho*, *meta*, and *para* substitution on phenyl rings to the ketone functional group as well as mono- or disubstitutions were also incorporated. The design served the purpose of investigating the scope of the chemistry and its robustness for library synthesis, as well as the effect of substituents on the phenyl rings for future optimization and SAR studies. As outlined in Scheme 2, synthesis of a small library of marinopyrrole **1c**−**1l** with different substituents on the phenyl rings was accomplished in yields of 5−49% in a four-step synthesis. It has been demonstrated that the chemistry can accommodate substituents on phenyl rings from strong electron donating groups (bis-methoxy, **1l**, **1m**) to electron withdrawing groups (trifluoromethyl, **1j**, **1k**) by addition of a variety of Grignard's reagents or organic lithium reagents to dialdehyde **7**. The alcohol intermediates were subjected to oxidation with CrO_3, followed by deprotection of the Ts group, and chlorination with NCS to furnish the desired product **1c**−**1m**. The chloro atom on the electron-rich phenyl rings in **1l** and **1m** was introduced unintentionally during chlorination of the corresponding precursor, but the outcome paves the avenue to access diversity of both phenyl rings with trisubstituents. Compound **1n** was not made because chlorination can not be avoided on the electron-rich bis-methoxyphenyl rings. Compound **1m** was obtained from **1l** by selective demethylation with BBr_3 in CH_2Cl_2 in high yield using a similar procedure for preparation of (±)-

1a from **1c**. Chlorination on the electron-rich phenyl rings also established a route for potential substitutions replacing chlorines if needed.

Although our current method has been limited to the generation of symmetrical compounds in terms of constitution and substituents on the two halves of the molecule as racemic materials, the convergent synthesis of intermediate **4** may allow de-symmetrization of the final target. Our efforts toward de-symmetrization of the final target and enantiomerically pure materials are ongoing, and the accomplishment of novel chemical entities based on marine natural product marinopyrrole will be realized if successful.

Conclusions

In summary, the first total synthesis of antibiotic natural product (±)-marinopyrrole A has been achieved via a nine-step synthesis in an overall yield of 30%. Spectroscopic data of (±)-marinopyrrole A synthesized in this study are consistent with those of **1a**, the naturally isolated product.[4a] The synthesis avails the natural product in good quantities as compared to an earlier biosynthetic effort that provided the material in only very limited amounts. Using this method, a focused library of (±)-marinopyrrole A derivatives was designed and synthesized to study the scope of chemistry and the feasibility for library synthesis. Since the parent compound (-)-marinopyrrole A displayed antibitotic and cytotoxicity, the chemistry developed in this report makes access to the natural product derivatives possible for SAR studies and further development. All compounds synthesized were fully characterized using ^{1}H and ^{13}C NMR, and high resolution mass spectrometry. The purity of the library compounds ranges from 95.0% to 99.4% and confirmed by high-performance liquid chromatography (HPLC). Design and synthesis of the next generation of marinopyrrole analogues have been ongoing. The use of combinatorial chemistry as a powerful tool to elaborate and speed up evaluation of marinopyrrole derivatives for both antibiotic and anticancer activities will be reported in due course.

Experimental Section

All chemicals were purchased from commercial suppliers and used without further purification. All solvents were dried and distilled before use. THF was distilled from sodium/benzophenone. Dichloromethane and acetonitrile were distilled over calcium hydride. Flash column chromatography was performed with silica gel (200−300 mesh). ^{1}H NMR spectra were recorded at 400 MHz at ambient temperature. ^{13}C NMR spectra were recorded at either 50 or 100 MHz at ambient temperature. Infrared spectra were recorded on a spectrophotometer (Perkin-Elmer Spectrum 100)). Melting points were determined with melting point apparatus (Fukai X-4)). High resolution mass spectra were performed by FAB method. The specifications of HPLC analysis are as follows: flow rate, 1 mL/min; column, Inertsil SIL, 5 μm, 4.6 × 250 mm; wavelength 254 nm; mobile phase, *n*-hexane/*iso*-propanol.

Diethyl 1′*H*-1,3′-bipyrrole-2,2′-dicarboxylate (4). To a solution of **2** (2.00 g, 10.50 mmol) in toluene (20 mL) were added α-ketone ester **3** (3.40 g, 15.74 mmol) and *p*-TSA (26 mg, 0.14 mmol). Ethyl 3-amino-1*H*-pyrrole-2-carboxylate hydrochloride (**2**)[8] and ethyl 4-(1,3-dioxan-2-yl)-2-oxobutanoate (**3**)[6] were prepared according to literature procedure. The mixture was then heated to reflux for 10 h. After cooling to room temperature, the mixture was adjusted to pH 7.0 with saturated aqueous $NaHCO_3$ and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (10% EtOAc/petroleum ether) to give **4** (2.40 g, 82% yield) as a light yellow solid. mp 70−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 4.10−4.19 (m, 4H), 6.26 (dd, J = 4.0, 2.8 Hz, 1H), 6.31 (t, J = 2.8 Hz, 1H), 6.89 (t, J = 1.6 Hz, 1H), 6.91 (t, J = 3.2 Hz, 1H), 7.07 (dd, J = 4.0, 2.0 Hz, 1H), 9.32 (br, s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.2, 59.6, 60.2, 108.5, 109.6, 117.4, 117.7, 120.6, 124.5, 129.7, 130.1, 160.1, 160.6 ppm; HRMS $(M+Na)^+$ calcd for $C_{14}H_{16}N_2NaO_4$ 299.1008, found 299.0987; IR (KBr) 3300, 2987, 1713, 1672, 1421, 1282, 1138, 733, 608 cm^{-1}.

Diethyl 1′-Tosyl-1′*H*-1,3′-bipyrrole-2,2′-dicarboxylate (5). To a solution of **4** (2.00 g, 7.25 mmol) in anhydrous CH_2Cl_2 (20 mL) were added 4-dimethylaminopyridine (DMAP, 4.40 g, 36.07 mmol) and *N*,*N*-diisopropylethylamine (DIPEA, 4.70 g, 36.43 mmol) at 0 °C. After being stirred for 10 min, TsCl (11.50 g, 72.33 mmol) was added to the mixture and allowed to stir for 8 h at room temperature. The mixture was extracted with CH_2Cl_2 (25 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (5% EtOAc/petroleum ether) to give **5** (2.96 g, 95% yield) as a light yellow solid. mp 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H), 2.44 (s, 3H), 3.97 (q, J = 7.2 Hz, 2H), 4.07 (q, J = 7.2 Hz, 2H), 6.22 (dd, J = 4, 2.8 Hz, 1H), 6.37 (d, J = 3.6 Hz, 1H), 6.81 (dd, J = 2.8, 2.0 Hz, 1H), 7.03 (q, J = 2.0 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 3.2 Hz, 1H), 7.93 (d, J = 8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 13.9, 21.6, 59.8, 60.9, 109.0, 111.1, 118.1, 120.7, 124.7, 125.3, 128.2, 128.2, 129.5, 129.5, 129.7, 134.3, 135.7, 145.1, 158.2, 160.1 ppm; HRMS $(M+Na)^+$ calcd for $C_{21}H_{22}N_2NaO_6S$ 453.1096, found 453.1097; IR (KBr) 3436, 3141, 2982, 1727, 1579, 1441, 1374, 1179, 1101, 1024, 748, 671, 591 cm^{-1}.

(1′-Tosyl-1′*H*-1,3′-bipyrrole-2,2′-diyl)dimethanol (6). To a solution of **5** (500 mg, 1.16 mmol) in anhydrous CH_2Cl_2 (15 mL) was slowly added DIBAL-H (4.67 mL, 1 M solution in toluene, 4.70 mmol) by syringe under N_2 at 0 °C. After being stirred for 6 h at room temperature, the mixture was quenched by addition of saturated aqueous Na_2SO_4. The resulting suspension was filtered. The filtrate was concentrated in vacuum, and then purified by column chromatography (33% EtOAc/petroleum ether) to give **6** (370 mg, 92% yield) as a white solid. mp 103−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.63 (br, s, 1H), 3.48 (br, s, 1H), 4.31 (s, 2H), 4.42 (s, 2H), 6.19 (t, J = 3.6 Hz, 1H), 6.29 (dd, J = 3.6, 1.6 Hz, 1H), 6.33 (d, J = 3.6 Hz, 1H), 6.63 (q, J = 1.6 Hz, 1H), 7.30 (d, J = 3.2 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz,

$CDCl_3$) δ 21.6, 52.3, 55.3, 108.6, 109.9, 111.4, 121.4, 124.2, 127.2, 127.7, 127.7, 130.1, 130.1, 130.1, 134.3, 135.5, 145.7 ppm; HRMS $(M+Na)^+$ calcd for $C_{17}H_{18}N_2NaO_4S$ 369.0885, found 369.0881; IR (KBr) 3324, 2928, 1646, 1592, 1453, 1375, 1148, 1087, 1006, 670, 602 cm^{-1}.

1′-Tosyl-1′*H*-1,3′-bipyrrole-2,2′-dicarbaldehyde (7). To a solution of diol **6** (2.90 g, 8.38 mmol) in anhydrous DMSO (20 mL) was added 2-iodoxybenzoic acid (IBX, 7.04 g, 25.14 mmol). After being stirred for 6 h at 70 °C, the mixture was allowed to cool to room temperature. The suspension was filtered, and the filtrate was extracted with EtOAc (50 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by column chromatography (12% EtOAc/petroleum ether) to give **7** (2.58 g, 90% yield) as a light yellow solid. mp 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 6.41 (dd, J = 4.0, 2.4 Hz, 1H), 6.45 (d, J = 3.2 Hz, 1H), 7.02−7.03 (m, 1H), 7.10 (dd, J = 4.0, 1.6 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 3.6 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 9.49 (s, 1H), 9.71 (s, 1H) ppm;^{13}C NMR (50 MHz, $CDCl_3$) δ 21.7, 111.3, 111.6, 124.1, 125.7, 127.5, 127.9, 127.9, 130.1, 130.1, 132.3, 133.0, 134.7, 136.6, 146.3, 177.2, 179.4 ppm; HRMS $(M+Na)^+$ calcd for $C_{17}H_{14}N_2NaO_4S$ 365.0572, found 365.0530; IR (KBr) 3444, 3137, 2923, 1668, 1562, 1447, 1361, 1180, 1014, 752, 668 cm^{-1}.

(±)-4,6-Bis(2-methoxyphenyl)-3-tosyl-4,6-dihydro-3*H*-dipyrrolo[2,1-*c*:3′,2′-e][1,4]oxazepine (9) and 1′-Tosyl-1′*H*-1,3′-bipyrrole-2,2′-diyl)bis((2-methoxyphenyl)methanone (10). Under N_2, the freshly prepared 2-methoxy phenylmagnesium bromide (4.94 g, 23.39 mmol) was added dropwise to a stirred solution of **7** (1.00 g, 2.92 mmol) in anhydrous THF (25 mL) at 0 °C. After being stirred for 5 h, the mixture was quenched by addition of a saturated aqueous solution of Na_2SO_4 (5 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4 and evaporated to give a yellow residue. Without purification, the residue was directly subjected to the oxidation by CrO_3 (1.17 g, 11.70 mmol) in anhydrous pyridine (15 mL) at room temperature. The reaction mixture was stirred for 4 h and then concentrated in vacuum. The residue was dissolved in EtOAc and filtered. The filter cake was washed by EtOAc (30 mL × 3). The combined organic layers were concentrated to give a residue, which was purified by column chromatography (12% EtOAc/petroleum ether) to give **10** (1.12 g, 69% yield) and **9** (157 mg, 10% yield). **1′-Tosyl diketone 10**: Light yellow solid, mp 113−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.68 (s, 3H), 3.75 (s, 3H), 5.83 (t, J = 3.2 Hz, 1H), 6.27 (d, J = 2.4 Hz, 1H), 6.43 (d, J = 3.6 Hz, 1H), 6.66−6.75 (m, 3H), 6.90 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 7.2 Hz, 1H), 7.23−7.26 (m, 1H), 7.33−7.36 (m, 4H), 7.57 (d, J = 3.6 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3, 55.5, 55.5, 109.3, 111.7, 111.9, 112.0, 119.7, 119.7, 119.7, 122.8, 125.4, 126.8, 128.0, 128.0, 128.7, 129.2, 129.9, 129.9, 130.6, 131.2, 132.0, 132.4, 132.5, 133.6, 135.7, 145.4, 156.5, 157.8, 182.6, 182.9 ppm; HRMS $(M+Na)^+$ calcd for $C_{31}H_{26}N_2NaO_6S$ 577.1409, found 577.1386; IR (KBr) 3451, 3139, 2926, 3843, 1646, 1596, 1487, 1412, 1367, 1176, 1020, 754 cm^{-1}. **Oxazepine 9**: Yellow solid, mp 193−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.75 (s, 3H), 3.79 (s, 3H), 5.31 (d, J = 1.6 Hz, 1H), 5.87 (s, 1H), 6.04 (t, J = 3.2 Hz, 1H), 6.54 (d, J = 3.6 Hz, 1H), 6.57 (td, J = 7.6, 0.8 Hz, 1H), 6.71 (dd, J = 7.6, 2.0 Hz, 1H), 6.83−6.89 (m, 3H), 6.95 (t, J = 7.6 Hz, 1H), 7.09 (t, J = 8.0 Hz, 2H), 7.16 (td, J = 8.4, 1.6 Hz, 1H), 7.27 (td, J = 8.4, 1.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 3H), 7.38 (d, J = 3.6 Hz, 1H), 7.49 (dd, J = 3.6, 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 55.3, 56.2, 68.8, 74.4, 107.0, 107.6, 108.5, 109.7, 111.6, 119.4, 120.4, 120.4, 122.9, 123.7, 126.6, 126.6, 127.8, 128.3, 128.4, 128.9, 129.2, 129.6, 129.6, 129.7, 129.9, 135.4, 136.9, 144.3, 155.7, 157.8 ppm; HRMS $(M+H)^+$ calcd for $C_{31}H_{29}N_2O_5S$ 541.1797, found 541.1800; IR (KBr) 3448, 2921, 2842, 1601, 1493, 1462, 1369, 1248, 1136, 1058, 745, 672 cm^{-1}.

1′*H*-1,3′-Bipyrrole-2,2′-diylbis(2-methoxyphenyl)methanone (11). To a solution of **10** (58 mg, 0.10 mmol) in a 1:1 mixture of MeOH/THF (2 mL) was added KOH (24 mg, 0.42 mmol) at room temperature. After being stirred for 1 h, the mixture was adjusted to pH 7.0 with 0.5 N HCl and extracted with EtOAc (10 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (14% EtOAc/petroleum ether) to give **11** (40 mg, 95% yield) as a light yellow solid. mp 175−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.80 (s, 3H), 5.81 (dd, J = 4.0, 2.8 Hz, 1H), 6.33−6.35 (m, 2H), 6.65 (dd, J = 2.8, 2.0 Hz, 1H), 6.69−6.72 (m, 2H), 6.93−6.97 (m, 2H), 7.07 (t, J = 3.2 Hz, 1H), 7.17−7.23 (m, 3H), 7.39 (td, J = 7.2, 1.6 Hz, 1H), 9.43 (br, s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.3, 55.6, 108.4, 110.6, 110.6, 111.4, 119.5, 119.9, 122.9, 123.2, 125.9, 128.0, 128.7, 129.0, 129.4, 129.7, 130.8, 130.9, 131.2, 132.3, 156.5, 157.1, 183.4, 183.8 ppm; HRMS $(M+Na)^+$ calcd for $C_{24}H_{20}N_2NaO_4$ 423.1321, found 423.1310; IR (KBr) 3363, 3069, 2934, 2841, 1625, 1491, 1437, 1407, 1250, 1164, 1027, 726 cm^{-1}.

1′*H*-1,3′-Bipyrrole-2,2′-diylbis(2-hydroxyphenyl)methanone (12). To a solution of **11** (50 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (2 mL) was slowly added BBr_3 (124 mg, 0.52 mmol) via a syringe under N_2 at −78 °C. After being stirred for 0.5 h, the mixture was quenched by addition of MeOH (0.5 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (12% EtOAc/petroleum ether) to give **12** (47 mg, 98% yield) as a yellow solid. mp 150−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (t, J = 2.8 Hz, 1H), 6.34 (t, J = 2.8 Hz, 1H), 6.46 (t, J = 8.0 Hz, 1H), 6.71 (dd, J = 4.0, 1.6 Hz, 1H), 6.77−6.80 (m, 2H), 6.91 (t, J = 2.8 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 2.8 Hz, 1H), 7.24−7.28 (m, 1H), 7.35 (dd, J = 8.0, 1.2 Hz, 1H), 7.40−7.45 (m, 2H), 9.73 (br, s, 1H), 11.03 (s, 1H), 11.56 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.4, 110.2, 117.5, 117.8, 118.5, 118.6, 119.0, 119.8, 123.2, 123.4, 123.5, 130.1, 130.4, 130.8, 131.5, 132.3, 135.3, 135.4, 161.5, 162.3, 187.7, 188.2 ppm; HRMS $(M+H)^+$ calcd for $C_{22}H_{17}N_2O_4$ 373.1188, found 373.1224; IR (KBr) 3345, 2962, 2923, 2855, 1623, 1584, 1555, 1409, 1256, 1096, 1028, 805

cm^{-1}. Purity was determined to be 97.1% by HPLC analysis using *n*-hexane/*iso*-propanol (95:5) as mobile phase.

(4,4′,5,5′-Tetrachloro-1′*H*-1,3′-bipyrrole-2,2′-diyl)bis(2-methoxyphenyl)methanone (1c). To a solution of **11** (400 mg, 1.00 mmol) in acetonitrile (5 mL) was added NCS (587 mg, 4.40 mmol) at 40 °C. After being stirred for 30 h, the mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (11% EtOAc/petroleum ether) to give **1c** (401 mg, 75% yield) as a light yellow solid. mp 193−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.79 (s, 3H), 6.32 (s, 1H), 6.68 (t, J = 7.2 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.96 (t, J = 7.6 Hz, 2H), 7.18 (dt, J = 7.2, 1.2 Hz, 2H), 7.25 (td, J = 8.0, 1.6 Hz, 1H), 7.41 (td, J = 8.0, 1.6 Hz, 1H), 9.76 (br, s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.5, 55.7, 110.4, 110.0, 111.6, 111.6, 119.7, 119.8, 120.2, 120.7, 124.0, 125.0, 125.7, 126.5, 127.9, 128.7, 129.3, 130.9, 131.6, 131.7, 156.6, 157.2, 182.4, 182.4 ppm; HRMS $(M+H)^+$ calcd for $C_{24}H_{17}Cl_4N_2O_4$ 536.9942, found 536.9940; IR (KBr) 3447, 2931, 2856, 1639, 1598, 1489, 1430, 1402, 1250, 1023, 929, 754, 646 cm^{-1}. Purity was determined to be 99.3% by HPLC analysis using *n*-hexane/*iso*-propanol (95:5) as mobile phase.

(±)-(4,4′,5,5′-Tetrachloro-1′*H*-1,3′-bipyrrole-2,2′-diyl)-bis(2-hydroxyphenyl)methanone (±)-1a. Compound (±)-**1a** was prepared according to the procedure for the preparation of **12** from **11** by using **1c** (100 mg, 0.19 mmol) and BBr_3 (187 mg, 0.75 mmol) to give a yellow solid (90 mg, 95% yield), which was purified by column chromatography (10% EtOAc/petroleum ether). mp 205−207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (t, J = 7.2 Hz, 1H), 6.71 (s, 1H), 6.88−6.93 (m, 2H), 7.02 (d, J = 8.4 Hz, 1H), 7.35 (td, J = 7.2, 1.2 Hz, 1H), 7.47−7.53 (m, 2H), 7.57 (dd, J = 8.0, 1.6 Hz, 1H), 10.00 (s, 1H), 10.42 (s, 1H), 11.20 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 110.6, 112.7, 117.7, 118.3, 118.6, 118.9, 118.9, 119.0, 120.3, 120.4, 123.2, 123.8, 124.1, 128.8, 130.3, 131.8, 136.1, 136.2, 161.0, 162.4, 185.9, 186.8 ppm; HRMS $(M+Na)^+$ calcd for $C_{22}H_{12}Cl_4N_2NaO_4$ 530.9449, found 530.9455; IR (KBr) 3302, 3247, 2923, 2854, 1622, 1592, 1441, 1406, 1257, 1026, 867, 764, 584 cm^{-1}. Purity was determined to be 97.8% by HPLC analysis using *n*-hexane/*iso*-propanol (95:5) as mobile phase.

General Procedure for Synthesis of Compound 1c−1m. Ketone (**11**) was prepared by addition of the corresponding Grignard's reagent or organic lithium reagent generated in situ to dialdehyde **7** (1 equiv) in *n*-pentane (lithium reagent, 8 equiv) or THF (Grignard's reagent, 8 equiv), followed by oxidation using CrO_3 (4 equiv) in pyridine. After purification by flash column chromatography, removal of Ts protecting group was carried out with KOH (4 equiv) in MeOH/THF (1:1). The corresponding intermediate after purification by flash column chromatography was chlorinated using NCS (4 equiv) in acetonitrile to furnish the desired product.

(4,4′,5,5′-Tetrachloro-1′*H*-1,3′-bipyrrole-2,2′-diyl)bis(phenyl)methanone (1d). (56 mg, 74% yield). mp 118−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (br, s, 1H), 6.44 (s, 1H), 7.10 (t, J = 6.8 Hz, 2H), 7.32 (t, J = 7.6 Hz, 1H), 7.37−7.43 (m, 4H), 7.47−7.55 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.6, 112.0, 120.6, 120.8, 123.7, 124.6, 124.7, 127.8, 127.8, 127.9, 127.9, 128.3, 128.3, 129.4, 129.4, 129.8, 131.8, 132.6, 136.9, 137.1, 183.5, 183.9 ppm; HRMS $(M+Na)^+$ calcd for $C_{22}H_{12}Cl_4N_2NaO_2$ 498.9551, found 498.9543; IR (KBr) 3442, 3211, 2930, 1637, 1399, 1240, 1013, 706 cm^{-1}. Purity was determined to be 99.3% by HPLC analysis using *n*-hexane/*iso*-propanol (95:5) as mobile phase.

(4,4′,5,5′-Tetrachloro-1′*H*-1,3′-bipyrrole-2,2′-diyl)bis(3-methoxyphenyl)methanone (1e). (24 mg, 56% yield). mp 56−59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.86 (s, 3H), 6.89 (s, 1H), 7.11−7.14 (m, 1H), 7.23−7.25 (m, 1H), 7.31 (dd, J = 2.0, 0.8 Hz, 1H), 7.36−7.47 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 55.5, 111.9, 112.0, 113.1, 113.6, 113.7, 114.4, 118.4, 118.8, 120.8, 121.8, 122.6, 123.9, 124.9, 129.3, 130.1, 130.2, 132.8, 138.8, 159.5, 160.0, 164.9, 183.1 ppm; HRMS $(M+K)^+$ calcd for $C_{24}H_{16}Cl_4KN_2O_4$ 574.9501, found 574.9504; IR (KBr) 3431, 2960, 2925, 1729, 1642, 1582, 1435, 1266, 1207, 1041, 806 cm^{-1}. Purity was determined to be 98.7% by HPLC analysis using *n*-hexane/*iso*-propanol (95:5) as mobile phase.

(4,4′,5,5′-Tetrachloro-1′*H*-1,3′-bipyrrole-2,2′-diyl)bis(4-methoxyphenyl)methanone (1f). (45 mg, 65% yield). mp 67−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 3.91 (s, 3H), 6.83 (s, 1H), 6.95−7.02 (m, 4H), 7.81−7.84 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 55.7, 111.3, 111.7, 112.7, 113.5, 113.7, 113.7, 114.7, 114.7, 118.0, 120.0, 123.7, 130.2, 130.5, 131.6, 131.6, 132.2, 134.0, 134.0, 163.2, 164.0, 165.6, 182.4 ppm; HRMS $(M+K)^+$ calcd for $C_{24}H_{16}Cl_4KN_2O_4$ 574.9501, found 574.9650; IR (KBr) 3448, 2925, 2847, 1722, 1600, 1510, 1438, 1258, 1172, 1026, 845 cm^{-1}. Purity was determined to be 99.2% by HPLC analysis using *n*-hexane/*iso*-propanol (95:5) as mobile phase.

(4,4′,5,5′-Tetrachloro-1′*H*-1,3′-bipyrrole-2,2′-diyl)bis(2-fluorophenyl)methanone (1g). (20 mg, 50% yield). mp 46−48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 7.16 (t, J = 8.8 Hz, 1H), 7.20−7.25 (m, 2H), 7.33 (t, J = 7.6 Hz, 1H), 7.48−7.54 (m, 2H), 7.65−7.75 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.3, 116.5, 116.9, 117.2, 121.2, 121.4, 124.0, 124.1, 125.0, 125.0, 130.4, 132.2, 133.0, 133.1, 136.7, 136.8, 158.5, 160.2, 161.0, 161.1, 162.8, 179.7 ppm; HRMS $(M+K)^+$ calcd for $C_{22}H_{10}Cl_4F_2KN_2O_2$ 550.9102, found 550.9101; IR (KBr) 3437, 2923, 2854, 1727, 1649, 1608, 1412, 1284, 1098, 925, 753 cm^{-1}. Purity was determined to be 96.0% by HPLC analysis using *n*-hexane/*iso*-propanol (95:5) as mobile phase.

(4,4′,5,5′-Tetrachloro-1′*H*-1,3′-bipyrrole-2,2′-diyl)bis(3-fluorophenyl)methanone (1h). (26 mg, 65% yield). mp 38−41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 7.30 (td, J = 8.4, 2.0 Hz, 1H), 7.41−7.54 (m, 3H), 7.55 (dd, J = 8.4, 2.8 Hz, 1H), 7.58−7.62 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.9, 116.1, 117.5, 117.7, 119.4, 119.6, 121.2, 122.6, 122.8, 124.9, 127.0, 129.6, 130.1, 130.2, 131.0, 131.1, 133.7, 139.5, 161.5, 163.7, 163.7, 181.9 ppm; HRMS $(M+K)^+$ calcd for $C_{22}H_{10}Cl_4F_2KN_2O_2$ 550.9102, found 550.9216; IR (KBr) 3132, 2963, 2632, 1794, 1732, 1645, 1588, 1441 cm^{-1}. Purity was determined to be 95.0% by HPLC analysis using *n*-hexane/*iso*-propanol (95:5) as mobile phase.

(4,4′,5,5′-Tetrachloro-1′*H*-1,3′-bipyrrole-2,2′-diyl)bis(4-fluorophenyl)methanone (1i). (27 mg, 67% yield). mp 48−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 7.17 (t, J = 4.8 Hz, 2H), 7.24 (t, J = 4.8 Hz, 2H), 7.83−7.92 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.5, 115.8, 116.7, 116.9, 120.8, 121.1, 125.1, 127.9, 129.9, 131.7, 131.8, 132.0, 132.1, 133.8, 134.1, 134.2, 163.8, 164.1, 165.8, 166.6, 168.4, 182.1 ppm; HRMS $(M+K)^+$ calcd for $C_{22}H_{10}Cl_4F_2KN_2O_2$ 550.9102, found 550.9116; IR (KBr) 3438, 3127, 2921, 1729, 1643, 1596, 1434, 1238, 1152, 850 cm^{-1}. Purity was determined to be 97.7% by HPLC analysis using *n*-hexane/*iso*-propanol (95:5) as mobile phase.

(4,4′,5,5′-Tetrachloro-1′*H*-1,3′-bipyrrole-2,2′-diyl)bis(2-(trifluoromethyl)phenyl)methanone (1j). (11 mg, 58% yield). mp 35−39 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (s, 1H), 7.48 (t, J = 3.6 Hz, 1H), 7.47−7.49 (m, 3H), 7.71 (t, J = 8.0 Hz, 1H), 7.74−7.77 (m, 2H), 7.88 (d, J = 7.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.7, 115.6, 119.8, 121.5, 122.4, 124.2, 126.8, 126.8, 127.6, 127.6, 128.0, 128.5, 129.6, 130.2, 130.6, 131.3, 132.1, 132.3, 133.1, 136.7, 136.7, 162.9, 162.9, 182.1 ppm; HRMS $(M+K)^+$ calcd for $C_{24}H_{10}Cl_4KN_2O_2$ 650.9038, found 650.8985; IR (KBr) 3449, 2924, 2855, 1738, 1649, 1421, 1316, 1277, 1126, 924, 770 cm^{-1}. Purity was determined to be 99.4% by HPLC analysis using *n*-hexane/*iso*-propanol (95:5) as mobile phase.

(4,4′,5,5′-Tetrachloro-1′*H*-1,3′-bipyrrole-2,2′-diyl)bis(4-(trifluoromethyl)phenyl)methanone (1k). (18 mg, 48% yield). mp 39−43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.77 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.0 Hz, 2H), 8.00 (d, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.6, 121.7, 121.7, 121.9, 124.4, 125.4, 125.5, 125.5, 125.5, 125.9, 126.3, 126.3, 126.3, 129.4, 129.4, 129.5, 129.6, 131.4, 131.4, 134.1, 136.3, 140.6, 164.1, 182.3 ppm; HRMS $(M+K)^+$ calcd for $C_{24}H_{10}Cl_4KN_2O_2$ 650.9038, found 650.9099; IR (KBr) 2954, 2923, 2853, 1737, 1645, 1436, 1323, 1133, 1065, 856, 678 cm^{-1}. Purity was determined to be 97.2% by HPLC analysis using *n*-hexane/*iso*-propanol (95:5) as mobile phase.

(4,4′,5,5′-Tetrachloro-1′*H*-1,3′-bipyrrole-2,2′-diyl)bis(5-chloro-2,4-dimethoxyphenyl)methanone (1l). (50 mg, 75% yield) mp 106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.81 (s, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 6.38 (s, 1H), 6.44 (s, 1H), 6.50 (s, 1H), 7.18 (s, 1H), 7.30 (s, 1H), 8.26 (br, s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 56.0, 56.3, 60.4, 95.8, 96.5, 111.6, 112.8, 112.9, 119.0, 120.0, 120.2, 120.7, 124.2, 125.2, 129.9, 130.7, 131.5, 157.6, 157.6, 158.0, 158.4, 178.1, 178.1, 180.2, 180.3 ppm; HRMS $(M+H)^+$ calcd for $C_{26}H_{19}Cl_6N_2O_6$ 664.9374, found 664.9387; IR (KBr) 3415, 3215, 2939, 1638, 1600, 1432, 1402, 1288, 1211, 1026, 612 cm^{-1}. Purity was determined to be 98.1% by HPLC analysis using *n*-hexane/*iso*-propanol (85:15) as mobile phase.

(4,4′,5,5′-Tetrachloro-1′*H*-1,3′-bipyrrole-2,2′-diyl)bis(5-chloro-2-hydroxy-4-methoxyphenyl)methanone (1m). (46 mg, 92% yield). mp 251−253 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 3.94 (s, 3H), 6.42 (s, 1H), 6.52 (s, 1H), 6.72 (s, 1H), 7.44 (s, 1H),7.46 (s, 1H), 9.77 (br, s, 1H), 11.13 (s, 1H), 11.77 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.5, 56.5, 100.4, 101.1, 110.5, 112.1, 112.5, 113.1, 113.2, 113.7, 119.8, 120.2, 122.7, 123.3, 123.7, 128.6, 131.1, 132.0, 161.1, 161.2, 163.2, 164.2, 183.6, 184.5 ppm; HRMS $(M+Na)^+$ calcd for $C_{24}H_{14}Cl_6N_2NaO_6$ 658.8881, found 658.8830; IR (KBr) 3305, 2920, 2851, 1624, 1582, 1443, 1276, 1060, 919, 783 cm^{-1}. Purity was determined to be 96.1% by HPLC analysis using *n*-hexane/*iso*-propanol (95:5) as mobile phase.

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Supporting Information Available. Detailed ^{1}H and ^{13}C NMR spectra, HPLC spectra, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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