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Synthetic Approaches to Regioisomerically Pure Porphyrins Bearing Four Different *meso*-Substituents

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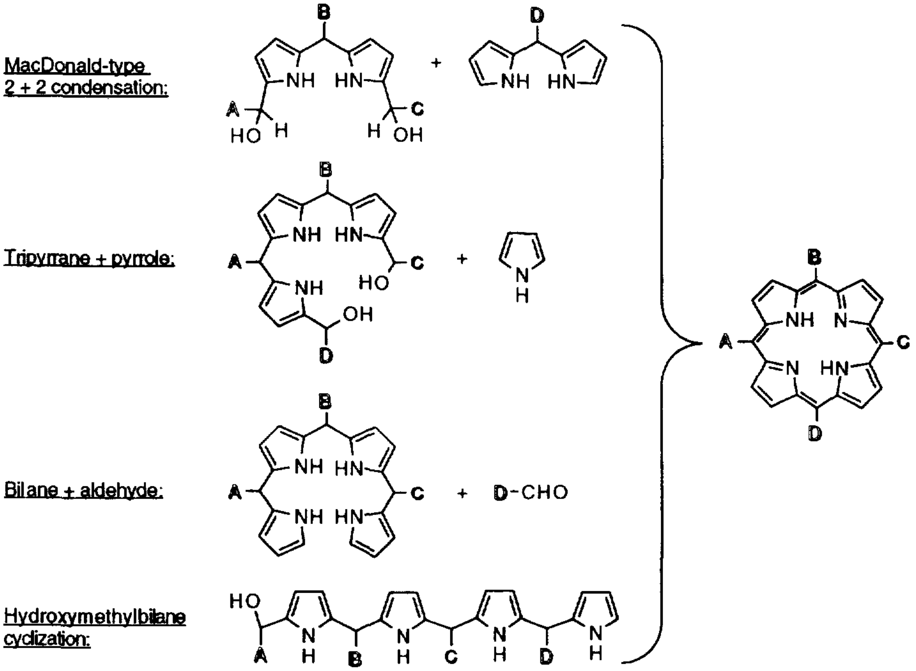
Abstract: Regioisomerically pure porphyrins bearing four different *meso*-substituents have been synthesized via a 9-step route starting from pyrrole and carbonyl-containing compounds. This synthesis builds on a one-flask synthesis of 1,9-unsubstituted dipyrromethanes. An acyl group is introduced selectively in the 1-position of the dipyrromethane by use of an acid chloride and the dipyrromethane Grignard reagent, which resembles the pyrrole Grignard reagent. In contrast to the 2- and 5-positions of a monomeric pyrrole, the 1- and 9-positions of a dipyrromethane are relatively non-interacting and can be functionalized independently. A 2-aryl-1,3-benzoxathiolium tetrafluoroborate, available from carbonyl containing compounds, serves as a latent acyl equivalent and alkylates regiospecifically the 9-position of a 1-acyldipyrromethane. Alternatively the 1- and 9-positions of a dipyrromethane can be functionalized independently by successive alkylations with two different 2-aryl-1,3-benzoxathiolium tetrafluoroborates. Hydrolysis of the mono or di(benzoxathiolyl)dipyrromethane followed by reduction of the 1,9-diacyl-dipyrromethane affords the corresponding dipyrromethane-diol. An acid-catalyzed MacDonald-type 2 + 2 condensation of the dipyrromethane-diol and a 1,9-unsubstituted dipyrromethane at room temperature followed by oxidation with DDQ gives the porphyrin bearing four different *meso*-substituents. The reaction sequence resulted in a single porphyrin isomer without acidolytic scrambling of the four *meso*-substituents. The porphyrin structures were confirmed by laser desorption mass spectrometry and by high field high resolution proton NMR spectroscopy. An entire synthesis can be performed in about two weeks. The controlled stepwise synthesis of porphyrins bearing four different *meso*-substituents should enable preparation of multi-functionalized porphyrin building blocks for application in the synthesis of bioorganic model systems.

The *meso*-substituted porphyrins occupy a central place in bioorganic chemistry.[3] Methods for the synthesis of *meso*-porphyrins still leave much to be desired, however, at least in comparison with design aspirations for creating sophisticated models of porphyrin-based enzymes, light-harvesting systems, or electron transport chains. A major limitation of available methods concerns the ability to place different substituents at the four *meso*-positions of the porphyrin. The major existing synthetic routes to *meso*-porphyrins can be summarized in a general way as follows:

- Porphyrins bearing four identical *meso*-substituents are available by condensation of an aldehyde and pyrrole.
- Porphyrins bearing two different types of *meso*-substituents can be prepared by a binary mixed aldehyde condensation. Alternatively, various methods can be employed that involve reaction at the 4 identical *meso*-sites of a porphyrin macrocycle. Both approaches are statistical in nature and usually require chromatographic separation of multiple porphyrin products.
- Trans-substituted porphyrins bearing two different groups can be prepared in a directed fashion by reaction of a dipyrromethane and an aldehyde.
- Porphyrins bearing four different *meso*-substituents can be prepared by a stepwise synthetic approach. We shall use the term ABCD-porphyrins to describe porphyrins bearing four different *meso*-substituents.

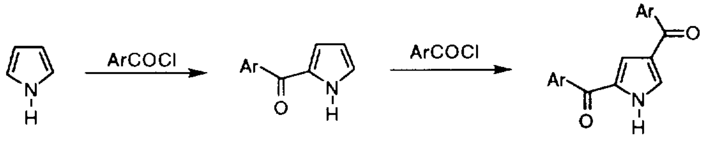
The synthesis of ABCD-porphyrins has only recently seen significant progress. Smith and coworkers described a synthesis of ABCD-porphyrins involving the acid-catalyzed condensation of two different dipyrromethanes in refluxing propionic acid.[4] However, acid-catalyzed cleavage of the dipyrromethanes and subsequent recombination resulted in the formation of undesired isomeric porphyrins. Ogoshi's group synthesized an ABCD-porphyrin in a similar manner.[5] A major difficulty in these routes to ABCD-porphyrins has little to do with macrocycle construction *per se* but instead involves problems associated with construction of the dipyrromethane components.

Retrosynthetic analysis shows several ways in which the synthesis of ABCD-porphyrins can be approached (Scheme 1). Other approaches are possible, of course, but the four shown represent distinct routes for the synthesis of ABCD-porphyrins. The synthesis of porphyrins bearing four different *meso*-groups presents problems somewhat different from those associated with the synthesis of naturally-occurring porphyrins. In the latter obtaining regiospecific orientation of the two different β-pyrrole substituents on each pyrrole is a central issue, but this is not a concern in the synthesis of porphyrins that lack β-substituents and are substituted solely with four different *meso*-substituents.



Scheme 1. Retrosynthetic analysis for synthesizing ABCD-porphyrins.

Regardless of which approach in Scheme 1 is taken, ultimately groups must be introduced into the pyrrole nucleus at the α and α'-positions in order to construct asymmetrically-substituted dipyrromethanes or longer oligo-pyrromethanes. Introducing acyl groups would be ideal, since pyrrole readily undergoes electrophilic aromatic substitution, but α,α'-functionalization with acyl units cannot be achieved in a direct manner (Scheme 2). Introduction of one acyl group at the 2-position proceeds smoothly, but attempts to introduce the second acyl group lead to substitution at the 4-position rather than the 5-position. An α-substituted pyrrole can be acylated at the α'-position as long as the α-substituent is not electron-withdrawing. Thus sequential introduction of groups at the α and α'-positions must involve electron-releasing groups preceding electron-withdrawing groups, as occurs with reactions such as alkylation followed by acylation. These problems of regiospecific substitution emerge at the stage of synthesizing dipyrromethanes, and indeed, preparing the dipyrromethane precursors has been the major bottleneck in carrying out approaches to ABCD-porphyrins.



Scheme 2. Problems with the attempted α,α'-acylation of pyrrole.

We recently discovered a one-flask synthesis of 1,9-unsubstituted, *meso*-substituted dipyrromethanes.[6] The acid-catalyzed reaction of an aldehyde dissolved in excess pyrrole in the absence of any other solvent affords the *meso*-substituted dipyrromethane in 47-86% yield. Pyrrole is an excellent solvent for diverse aldehydes and this method appears to have general applicability. The dipyrromethanes are relatively stable compounds and can be chromatographed, crystallized, and handled without special precautions. Other one-flask[7] or stepwise[4,6,8] syntheses of 1,9-unsubstituted, *meso*-substituted dipyrromethanes also have been developed. The general availability of these dipyrromethanes has prompted us to investigate methods for functionalizing the dipyrromethanes such that they can be used in rational syntheses of ABCD-porphyrins. Asymmetrically-substituted dipyrromethanes are essential intermediates in the synthesis of ABCD-porphyrins in each of the routes shown in Scheme 1. The MacDonald-type 2 + 2 condensation[9] employs dipyrromethanes directly, and the preparation of tripyrranes, bilanes, or higher oligomeric pyrroles also could proceed via a dipyrromethane intermediate. In this paper we outline the approaches we have been investigating for the rational synthesis of regioisomerically pure ABCD-porphyrins by extension of this chemistry of dipyrromethanes.

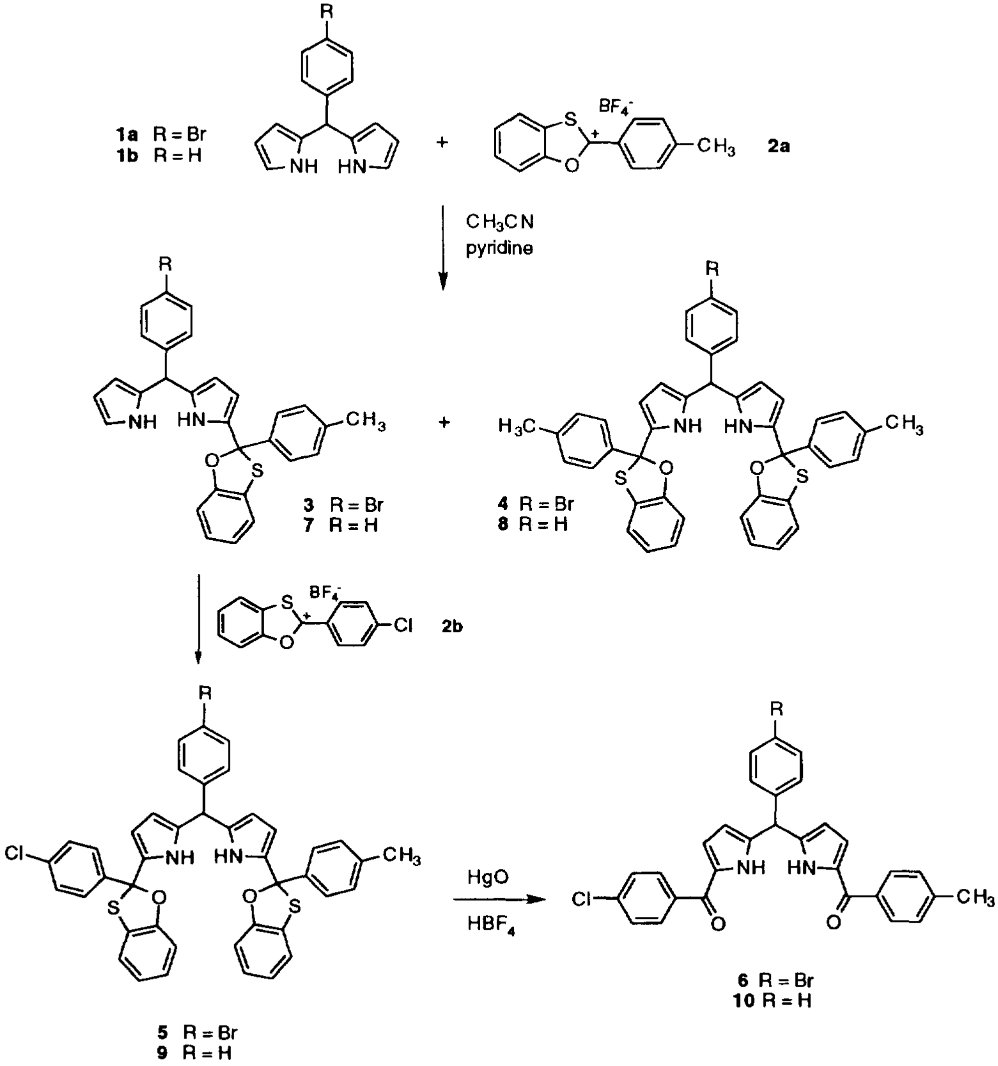
RESULTS AND DISCUSSION

Routes to 1,5,9-trifunctionalized dipyrromethanes:

Pyrrole can be acylated regioselectively at the 2-position by Friedel-Crafts acylation using an acid chloride and Lewis acid, or by treatment of the pyrrole Grignard reagent with an acid chloride.[10] In addition, Barbero *et al.* have shown that pyrrole can be alkylated in controlled fashion at the 2- and 5-positions with carbocationic benzoxathiolyl groups as masked acyl synthons.[11] This di-alkylation proceeds in striking contrast to the regiochemistry found upon direct di-acylation of pyrrole (Scheme 2). The benzoxathiolyl chemistry was particularly attractive to us as it provided a means of introducing acyl units at the pyrrolic α and α'-positions. We have extended these well-known alkylation and acylation reactions of pyrrole to dipyrromethanes, thereby achieving direct syntheses of asymmetrically-substituted dipyrromethanes. The ultimate regiochemistry of the resulting ABCD-porphyrin is controlled by the sequence of groups introduced in the dipyrromethane nucleus.

A) Alkylation with benzoxathiolium salts

Treatment of *meso*-(4-bromophenyl)dipyrromethane (**1a**)[6] with 2-(*p*-tolyl)-1,3-benzoxathiolium tetrafluoroborate (**2a**)[12] at room temperature in anhydrous acetonitrile containing pyridine gave the mono-alkylated product (**3**) in 67% yield and the dialkylated product (**4**) in 5.1% yield (Scheme 3). This reaction is quite clean, with the sole products consisting of residual starting dipyrromethane and the mono and di-alkylated products. Chromatographic workup on silica (hexanes/ethyl acetate/triethylamine, 80:20:2) afforded the desired mono-alkylated product.



Scheme 3. Successive alkylation as a route to asymmetrically di-acylated dipyrromethanes.

We found that using the dipyrromethane in a 3-fold excess afforded the mono-alkylated **3** with only a trace of the di-alkylated product, thereby facilitating the workup. Excess unreacted dipyrromethane **1a** was easily recovered upon column chromatography of the reaction mixture. The dipyrromethane alkylations were run at about one-fifth the concentration (44 mM of **2a**) of those of Barbero *et al.*,[11] affording rather clean reaction mixtures. When high concentrations were used, many other side products were formed. The reactions were rapid and were normally worked-up after 20 min to avoid the formation of undesired side products.

Repetition of this alkylation reaction with the 1-alkylated dipyrromethane (**3**) and a different benzoxathiolium salt (**2b**) afforded the 1,9-asymmetrically-alkylated dipyrromethane **5** in quantitative yield. In many respects of implementation, product distribution, and workup this alkylation of dipyrromethanes resembles that with pyrrole.[11] The acyl masking groups were removed by oxidative hydrolysis of **5** in the presence of aqueous HBF_4/HgO following the method of Barbero *et al.*,[11] affording the 1,9-diacyl-dipyrromethane **6** in 73% yield after column chromatography. It should be noted that before the reaction mixture from any of the above three reactions can be loaded on the silica column, the column must be washed with the basic eluant since dipyrromethane compounds otherwise will decompose on silica due to its acidity. Gravity elution affords good separation in about 2~3 h. This same reaction sequence was performed with *meso*-(phenyl)dipyrromethane (**1b**), affording the asymmetric diacyl-dipyrromethane **10**.

The stability of dipyrromethanes decreases in the series dipyrromethane > mono-acyl-dipyrromethanes ~ diacyl-dipyrromethanes > mono-alkylated dipyrromethane > di-alkylated dipyrromethane. The parent dipyrromethanes in the solid form are stable for weeks on the open benchtop and for months at -5 °C. At the other extreme, the solid mono-alkylated or di-alkylated dipyrromethanes begin to show signs of decomposition (~5% byproducts formed) within several hours in air on the benchtop, while solutions of these compounds turn brown within an hour. The diacyl-dipyrromethanes are stable for a few days on the open benchtop. However, the functionalized dipyrromethanes can be stored for months without discoloration as the dry solid at -5 °C. Given their relative instability, we usually quickly store the functionalized dipyrromethanes at -5 °C after chromatographic separation and vacuum removal of the solvent, and only perform limited analyses. The mono- and di-alkylated dipyrromethanes were characterized by TLC, ^{1}H NMR spectroscopy and high resolution mass spectrometry. The mono- and diacyl-dipyrromethanes were characterized by TLC, ^{1}H NMR spectroscopy, high resolution mass spectrometry and elemental analysis. These methods provide adequate analytical evidence of the expected structure of these intermediates; more thorough analyses are possible upon isolation of the ABCD-porphyrin which generally is far more stable than the precursor dipyrromethanes.

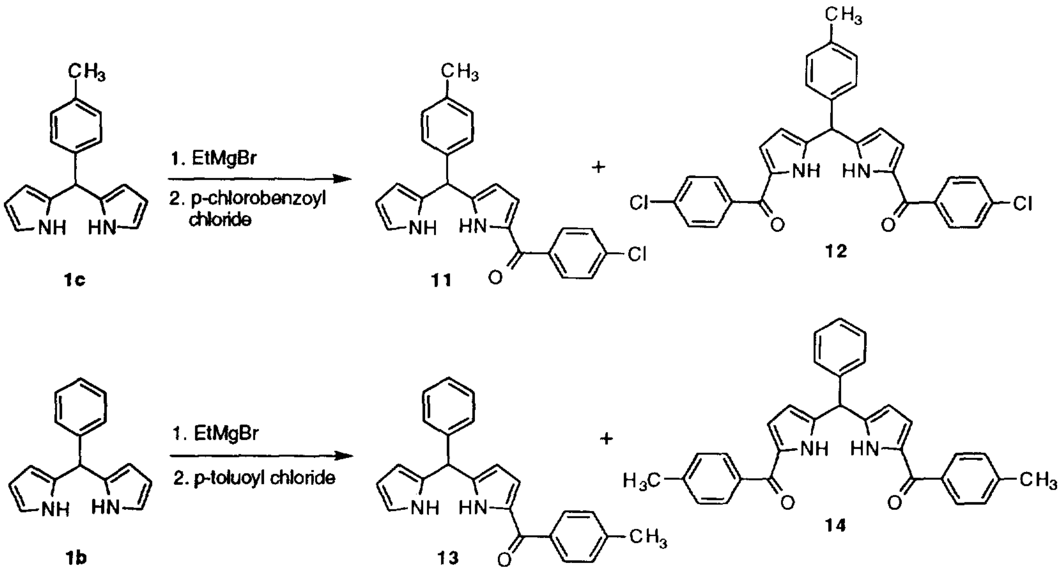
B) Acylation with dipyrromethane Grignard reagents

Alternative synthetic routes to asymmetrically-substituted dipyrromethanes such as **6** and **10** also were investigated. The benzoxathiolium tetrafluoroborates provide a mild means of introducing groups at the 1 and 9-positions of dipyrromethanes, which is not surprising since pyrrole can be similarly functionalized at the 2- and 5-positions. We felt that with dipyrromethanes the 1 and 9-positions could be functionalized independently with acyl groups, thus we investigated acylation reactions of dipyrromethanes.

Meso-(*p*-tolyl)dipyrromethane (**1c**) was treated with 2 moles of ethyl magnesium bromide in THF at room temperature (Scheme 4). The resulting bis-Grignard reagent of **1c** was then treated with *p*-chlorobenzoyl chloride, affording a mixture of the mono-acylated **11** and di-acylated **12**. These acyl-dipyrromethanes were isolated by column chromatography with gradient elution. A few experiments were performed to identify the appropriate ratios of ethyl magnesium bromide, dipyrromethane, and acid chloride for obtaining preferentially the mono-acylated product (Table 1). With only one mole of ethyl magnesium bromide per dipyrromethane little acylation occurred and the dipyrromethane was recovered intact. The best conditions we found with this limited study involve the use of 2.2 moles of ethyl magnesium bromide per dipyrromethane and 1.4 moles of the acid chloride. This reaction can be used with various dipyrromethanes as shown in Scheme 4.

Table 1. Effect of the molar ratios of starting materials on acylated dipyrromethane yields.

molar ratios of			dipyrromethane products	
dipyrromethane	EtMgBr	acid chloride	mono-acyl	di-acyl
1 (**1b**)	2.2	1.4	63% (**13**)	19% (**14**)
1 (**1b**)	1	1	13% (**13**)	trace (**14**)
1 (**1b**)	3	2.2	41% (**13**)	33% (**14**)
1 (**1c**)	2.4	2	24% (**11**)	24% (**12**)



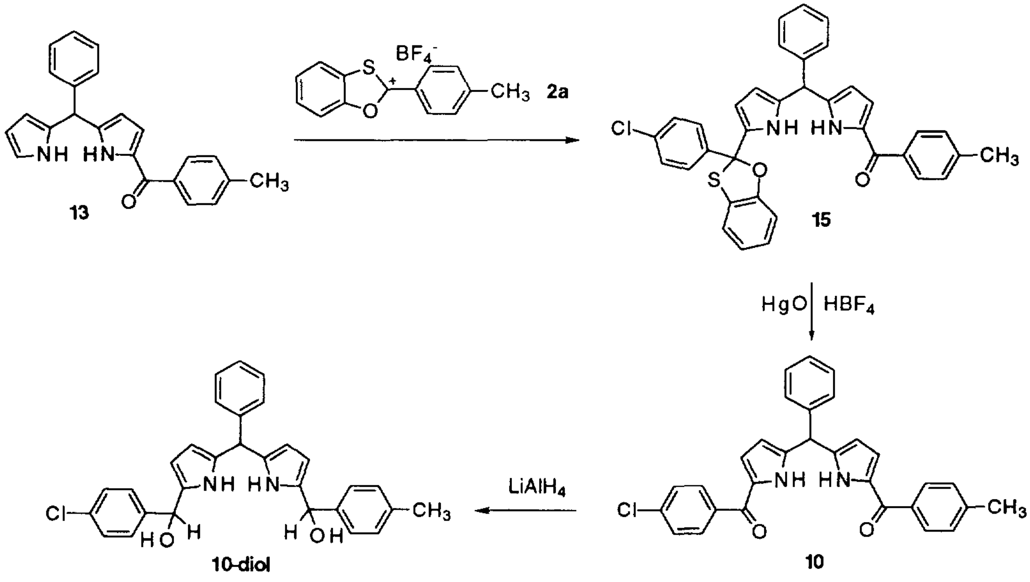
Scheme 4. Routes to mono- and di-acyl dipyrromethanes via dipyrromethane Grignard reagents.

The ^1H NMR spectra of mono- and di-acyl dipyrromethanes have distinctive features that make their identification straightforward. The pyrrolic protons in mono-acylated **11** show five sets of multiplets while those in the symmetrically-diacylated **12** show only two sets of multiplets.

Following the introduction of one acyl unit via the dipyrromethane Grignard reagent, alkylation can be used to introduce a second moiety into the dipyrromethane nucleus. Thus alkylation of 1-acyldipyrromethane

(**13**) with 2-(*p*-chlorobenzyl)-1,3-benzoxathiazolium tetrafluoroborate (**2a**) afforded **15** in 98% yield (Scheme 5). Treatment of **15** with HgO/HBF_4 in THF afforded the dipyrromethane bearing two different acyl moieties (**10**). The polarity imparted by the carbonyl group in conjunction with the appropriate solvent system facilitates chromatographic separation of the mono-acyl dipyrromethanes. Consequently, the acylation-alkylation reaction sequence provides a cleaner route for introducing acyl moieties at the 1 and 9-positions of dipyrromethanes (at least with the non-polar compounds investigated here) than the successive alkylation with benzoxathiolium salts as shown in Scheme 3.

The successful alkylation of **13** illustrates the independent reactivity of the two pyrrole nuclei in the dipyrromethane. Attempts to alkylate a 2-acylpyrrole would afford the 4-alkylated 2-acylpyrrole. In the dipyrromethane the pyrrole bearing the 1-acyl group is deactivated yet the alkylation occurs smoothly at the distant 9-position.

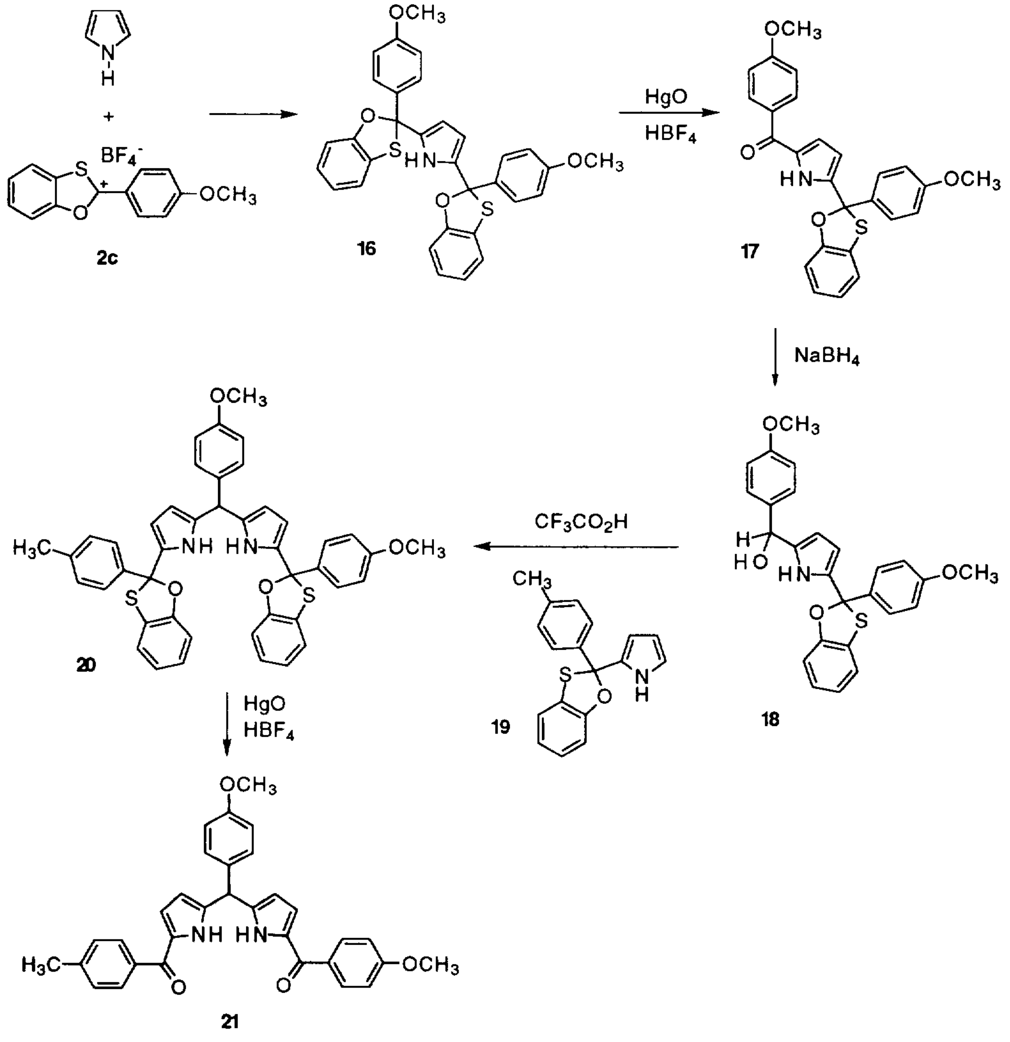


Scheme 5. Acylation-alkylation route to a dipyrromethane bearing two different acyl moieties.

C) Stepwise syntheses of dipyrromethanes

Prior to our finding of a one-flask synthesis of dipyrromethanes we focused on developing a stepwise synthesis of diacyl-dipyrromethanes. This route, outlined below, is laborious but may find applications where control is sought over the sequence of pyrrole units in the construction of the dipyrromethane (Scheme 6). The synthesis of pyrroles bearing one or two benzoxathiolyl groups, as described by Barbero *et al.*,[11] provides the point of departure for this synthesis. Treatment of a THF-suspension of **16** (available from pyrrole and **2c**)[11] with 0.5 equiv HgO followed by workup immediately after the suspension dissolved yielded the mono-deprotected **17** in 89% yield. Reduction with $NaBH_4$ gave the alcohol **18**. Condensation of **18** (0.012 M) and **19** (0.01 M) in the presence of mild acid catalysis afforded the di-alkylated dipyrromethane **20** in 53% yield. The condensation conditions are similar to those used in the one-flask condensation of pyrrole and aldehydes giving *meso*-porphyrins.[13] A controlled level of acid catalysis is essential for successful alkylation. No reaction occurred in CH_2Cl_2 with 0.1 or 0.01 M acetic acid at room temperature, the alcohol **18** decomposed with 0.01 M trifluoroacetic acid (TFA) at 0 °C, but reaction occurred smoothly with 10^{-3} M TFA at 0 °C for 1 h affording **20**. Deprotection of **20** with HgO/HBF_4 afforded the diacyl-dipyrromethane **21** in 92% yield.

The yields are generally high in this route (Scheme 6), but the stepwise synthesis of an asymmetrically-substituted diacyl-dipyrromethane requires a total of 8 steps (from pyrrole and carbonyl compounds) compared with only 6 steps for the route involving successive alkylation of a dipyrromethane (available via a one-flask synthesis). However the ability to prepare 1,9-difunctionalized dipyrromethanes in a stepwise manner may offer advantages for use with substituted or labeled pyrroles.



Scheme 6. Stepwise synthesis of dipyrromethanes bearing two different acyl moieties.

It is noteworthy that in the synthesis of trifunctionalized dipyrromethanes several diastereomers can be formed. Thus each dipyrromethane bearing benzoxathiolyl groups at the 1- and 9-positions such as **5**, **9**, or **20**, and each dipyrromethane-diol such as **6-diol** and **10-diol**, has 3 chiral centers. Upon formation of the porphyrin the 1-, 5-, and 9-positions are transformed into the *meso*-positions and in so doing chirality at these positions is lost.

Syntheses of porphyrins using functionalized dipyrromethanes:

A) 2 + 2 condensation for the synthesis of ABCD-porphyrins

The convenient availability of asymmetric 1,9-diacyl-dipyrromethanes makes possible a MacDonald-type 2 + 2 condensation for the synthesis of ABCD-porphyrins. This approach requires conversion of the 1,9-carbonyl groups to 1,9-hydroxymethyl groups, followed by acid-catalyzed condensations of the so-formed pyrrole-carbinols with a 1,9-unsubstituted dipyrromethane. We and others have shown that pyrrole-carbinols react with pyrrole under mild acidic conditions in high yield.[6,14]

The 1,9-diacyl-dipyrromethanes (**6**, **10**) were reduced with $NaBH_4$ to the corresponding di-(α-hydroxymethyl) compounds **6-diol** and **10-diol**, which are bright yellow compounds. Complete reduction was achieved as indicated in the IR spectra by the disappearance of the carbonyl stretch at ~1600 cm^{-1} and the appearance of a hydroxy stretch at ~3340 cm^{-1}. In addition, TLC (silica, hexanes/ethyl acetate/triethylamine, 66:33:2) showed complete conversion to the diol (diacyl-dipyrromethane R_f ~0.7, dipyrromethane-diol R_f ~0.3) with no observable side products. Upon exposure to air at room temperature, the dipyrromethane-diols began to turn brown within 30 min. Therefore, upon workup each dipyrromethane-diol was used immediately in a condensation with *meso*-(*p*-iodophenyl)dipyrromethane **1d** under conditions similar to those in the room temperature porphyrin synthesis.[6,13]

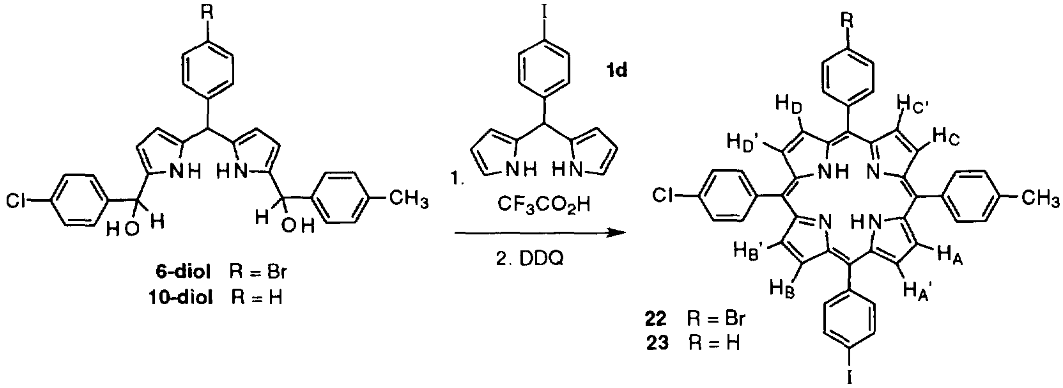
Prior to performing the 2 + 2 condensation of a dipyrromethane-diol and a dipyrromethane, we sought to establish reaction conditions that would give efficient reaction without concomitant acidolysis of the dipyrromethanes. The acid-catalyzed cleavage and reformation of polypyrranes is a well-known problem in porphyrin chemistry[15] and must be avoided in this approach to avoid scrambling the desired regioisomeric pattern of ABCD groups. We performed several omission experiments where 10 mM solutions of a dipyrromethane-diol or of a dipyrromethane in $CHCl_3$ were exposed to various acidic conditions, then samples were removed and treated with DDQ so that any porphyrinogen or related cyclic structures would be converted to the porphyrin.[13] The observation of any porphyrin detected spectroscopically thus indicates an undesirable level of acidolysis of the dipyrromethane compound. The studies are outlined below.

1) A solution of **6-diol** or **10-diol** turned deep red immediately upon exposure to 8.25 mM $BF_3{\cdot}O(Et)_2$, however, removal of aliquots over a period of 2 h and oxidation with DDQ showed no porphyrin formation.
2) Similar treatment (6.6 mM $BF_3{\cdot}O(Et)_2$) of *meso*-(*p*-iodophenyl)dipyrromethane **1d** gave an immediate red solution and a 12% yield of porphyrin after 20 min upon oxidation with DDQ. There was no detectable residual aldehyde in the dipyrromethane material, thus the observation of porphyrin can only be due to acidolysis of the dipyrromethane and subsequent condensation and cyclization.

3) Treatment of **6-diol** or **10-diol** with 33 mM, 56 mM or 112 mM TFA gave immediate formation of a green solution which turned red within 30 sec. As with $BF_3 \cdot O(Et)_2$, no porphyrin was observed over a 2 h period.

4) Treatment of **1d** with 10 mM, 33 mM or 56 mM TFA gave immediate formation of a light green solution which turned red within 30 sec, with no porphyrin observed within 1 h. At 112 mM TFA no porphyrin was detected after 30 min but a clearly discernible yield of 0.2% was observed at 40 min. The identity of the green species is not known, but it cannot be ruled out that it originates from a trace impurity or higher oligopyrromethane.

These studies show that $BF_3 \cdot O(Et)_2$ causes acidolysis of the 1,9-unsubstituted dipyrromethane and would be detrimental to the construction of a regioisomerically pure ABCD-porphyrin. TFA is a superior catalyst and at concentrations up to ~0.05 M does not cause significant acidolysis of the starting dipyrromethanes. Accordingly, the condensation of **6-diol** with **1d** (10 mM each) was performed using 56 mM TFA at room temperature. After 20 min DDQ was added to cause oxidation. Porphyrin **22** was isolated in 14% yield. Porphyrin **23** was obtained in 13% yield upon condensation of **10-diol** with **1e** under the same conditions (Scheme 7). Mass spectral and ^1H NMR spectroscopic data (vide infra) obtained for **22** and **23** were consistent with the expected structures and showed each to consist of a single isomer. The mass spectrum of each showed an intense parent ion with no peaks characteristic of rearranged porphyrins. In each case a single porphyrin regioisomer was obtained, with no observable acidolysis of the dipyrromethanes **6-diol**, **10-diol** or **1d** under the conditions for these 2 + 2 condensations. Although the yield in the porphyrin condensation is not high, this condensation is useful for the synthesis of regioisomerically pure ABCD-porphyrins.



Scheme 7. 2 + 2 condensation in the synthesis of ABCD-porphyrins.

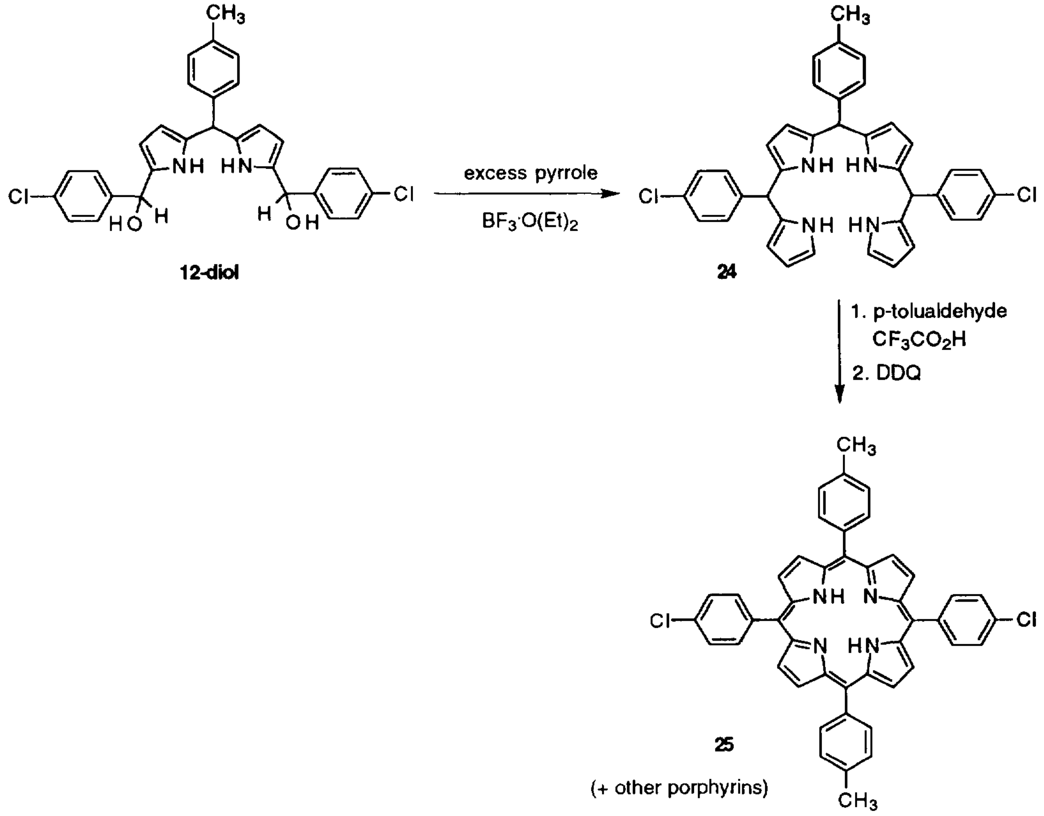
When the 2 + 2 condensation of 10 mM **6-diol** and **1d** was performed with 112 mM TFA for 20 min followed by oxidation with DDQ, the yield of porphyrin was 36%. A single porphyrin band was obtained by column chromatography, but this compound was found to be impure. The mass spectrum showed a smattering of peaks in the vicinity of the intense parent ion (867 amu) that could be assigned to exchange products, including 895 amu (*p*-phenyl substituents: I, I, CH_3, CH_3), 846 (I, Br, CH_3, CH_3), 820 (Br, Br, Cl, CH_3), 802 (I, Cl, CH_3, CH_3), and 755 (Br, Cl, CH_3, CH_3). The integrated area of the peaks corresponding to these exchange products was about equal to that of the parent ion. Similar results were observed upon condensation in the presence of 8.25 mM $BF_3{\cdot}O(Et)_2$. Condensation of **10-diol** and **1d** in the presence of 8.25 mM $BF_3{\cdot}O(Et)_2$ also gave a single porphyrin band but this was observed to be impure. The mass spectrum showed the intense parent ion (788.4) as well as peaks at 881 (I, I, CH_3, H), 768 (I, CH_3, CH_3, H), 754 (I, CH_3, H, H), 697 (Cl, Cl, CH_3, H), 678 (Cl, CH_3, CH_3, H), 662 (Cl, CH_3, H, H), 642 (CH_3, CH_3, H, H), and 628 (CH_3, H, H, H). A few of these peaks in principle could represent daughter ions, though no such peaks are observed with the porphyrin obtained in the condensation at lower acid concentrations. These results clearly reflect acidolytic scrambling of the *meso*-substituents. The NMR spectra of these samples also indicated they were not pure. In each case the inner NH proton peak was broadened in a steplike fashion. Though the NH peak of porphyrins typically is broad but smooth, the choppy peak shape clearly represented multiple components. NMR spectra collected at 55 °C did not give coalescence of the NH peaks as would be expected if the broadening were due to NH tautomerism.[16] At least for the compounds investigated here, a craggy broadening of the porphyrin NH peak has been a clear indicator of an impure sample of porphyrins.

A few experiments were performed in an effort to improve the yields of the 2 + 2 condensation, using the reaction of **10-diol** and **1d** as a test case. Variations of the [dipyrromethane] from 3-30 mM each with [TFA] from 6-20 mM gave no yields higher than 6% after 20 min. When acetic acid (0.01 M) was used as catalyst in the reaction of **10-diol** and **1d** at 5 mM each, no porphyrin was formed after 1 h. With trichloroacetic acid (0.01 M) the yield of porphyrin was 6.3% after 20 min. Further studies are required to identify conditions that afford higher yields while not causing acidolysis.

B) Preparation of a bilane and reaction with an aldehyde

Previously we showed that reaction of 2-[(α-hydroxy-α-phenyl)methyl]pyrrole with excess pyrrole at room temperature in the absence of solvent afforded *meso*-phenyldipyrromethane in 95% yield.[6] The high yield and mild conditions of this reaction suggested that a similar approach could be pursued with a dipyrromethane-diol, thereby affording a simple synthesis of a bilane (Scheme 8). The dipyrromethane **12-diol** was dissolved in pyrrole (80 equiv) and treated with a catalytic amount of $BF_3{\cdot}O(Et)_2$, the same conditions used in the one-flask synthesis of dipyrromethanes. After 10 min at room temperature the reaction mixture was worked up and the resulting bilane (**24**) was purified by chromatography. The bilane was isolated as a slightly off-white solid that was stable in air at room temperature for a few hours.

Treatment of the bilane (**24**) with *p*-tolualdehyde under the conditions for the 1-flask synthesis of porphyrins (10 mM each) via a pyrrole-aldehyde condensation gave porphyrin in yields varying from 6% (5 mM TFA) to 34% (33 mM TFA). However, mass spectral (and proton NMR) data showed the isolated porphyrin to be impure in both cases, consisting of the target **25** (713.7 amu), *meso*-tetrakis(*p*-tolyl)porphyrin (693.0), and the porphyrin bearing three *p*-tolyl and one *p*-chlorophenyl groups (671.9). Further studies are required to identify condensation conditions for performing this reaction. If successful, this route probably would not afford any particular advantage over the 2 + 2 condensation. However, the ability to prepare bilanes illustrates the synthetic versatility provided by the 1,9-diacyl-dipyrromethanes, and may provide access to synthetic bile pigments and related chromophores,[17] as well as longer oligopyrromethanes.



Scheme 8. Preparation of a bilane and its attempted conversion to a porphyrin.

High resolution proton NMR study of ABCD-porphyrins:

To unveil the proton couplings and unambiguously assign each peak in the NMR spectrum of ABCD-porphyrins, we conducted a 620.2 MHz high field high resolution proton NMR study with Zn(II)-5-(*p*-chlorophenyl)-10-phenyl-15-(*p*-tolyl)-20-(*p*-iodophenyl)porphyrin (**Zn-23**). A zinc porphyrin was chosen to eliminate the inner core NH tautomerism and consequent broadening of the β-pyrrole proton peaks. All the spectra were obtained using a dilute solution of **Zn-23** (~3 mM) in carbon disulfide, with 0.5% TMS and 0.5% dioxane-d_8 added as reference and lock.

In Fig. 1 are displayed 100-Hz sections of the spectrum, showing all aromatic peaks. The peak from the methyl group of the *p*-tolyl moiety was also observed as an unresolved multiplet and it provided no additional information. Thus coupling constants of the methyl group and the adjacent protons were not determined. All signals in the spectrum were assigned and confirm the predicted structure. The group of eight doublets (four AB-type spectra) in the region 5430 to 5480 Hz from TMS (δ 8.75 to δ 8.84) arise from the eight pyrrole protons (labeled H_A, $H_{A'}$...H_D, $H_{D'}$ in order of assignment from low to high field; Scheme 7), as confirmed by their characteristic chemical shifts and coupling constants (Table 2). In Fig. 2, the COSY spectrum covering the same range as the 1-D spectra showed clearly the cross-peaks identifying the four AB systems.

Table 2. Chemical shifts and observed splittings of aromatic protons of **Zn-23** at 620.2 MHz.

Proton	δ (ppm)	$J + D$ (Hz)
Pyrrole protons		
H_A, $H_{A'}$	8.807, 8.794	4.52
H_B, $H_{B'}$	8.808, 8.772	4.52
H_C, $H_{C'}$	8.829, 8.782	4.54
H_D, $H_{D'}$	8.800, 8.773	4.50
Substituted phenyl protons		
p-methyl: H_o, H_m	7.964, 7.473	7.72
p-iodo: H_o, H_m	7.867, 8.018	7.62
p-chloro: H_o, H_m	8.049, 7.656	7.99
phenyl: H_o, H_m, H_p	8.083, 7.667, 7.691	*om* 7.23, *op* 1.73
		oo' 1.90, *mp* 8.04
		om' 0.63, *mm'* 1.48

The proton signals arising from the four *meso*-aryl groups were identified in part from their characteristic splitting patterns. The phenyl group, with signals at δ 8.083, δ 7.667 and δ 7.691, gave a complex second order splitting pattern which was simulated using the LAOCOON-type simulation program distributed by Varian Associates as part of the ADS-4000 operating system. An excellent fit was obtained with the splitting parameters given in Table 2, and the splittings are all within a few hundredths of those given in the literature for the aromatic protons of benzene, diphenyl, etc.[18] The aromatic protons of the *p*-tolyl group were identified by the presence of small long-range splittings arising from the *p*-methyl group. The *p*-chlorophenyl and *p*-iodophenyl protons gave characteristic A_2B_2 patterns, which were analyzed using the established methods given in the literature.[19] The COSY spectrum (Fig. 3) confirmed the couplings between the phenyl *o*- and *m*-protons and between the tolyl *o*- and *m*-protons, and identified the remaining two A_2B_2 spectra belonging to the *p*-chlorophenyl and *p*-iodophenyl groups. These were assigned on the basis of comparisons of the chemical shifts of the four systems of aryl protons with the shifts of benzene, toluene, chlorobenzene and iodobenzene.[18] In each case the chemical shift of the *o*-protons in the *meso*-aryl groups was 0.80 to 0.85 ppm further from TMS than that in the monocyclic model, while the *m*-protons gave signals 0.36 to 0.40 ppm further from TMS than did the corresponding protons in the monocyclics. These downfield shifts are in accord with expectation based on the anisotropic magnetic susceptibility of the porphyrin ring.

Finally a NOESY spectrum (Fig. 4) was recorded to establish the proximity of the various pyrrole protons to the *meso*-aryl groups. Because of the overlap of several of the pyrrole proton resonances, the assignment was not without difficulty. However, only one arrangement could be accommodated with the clearly resolved cross-peaks. The assignment is shown in Table 2.

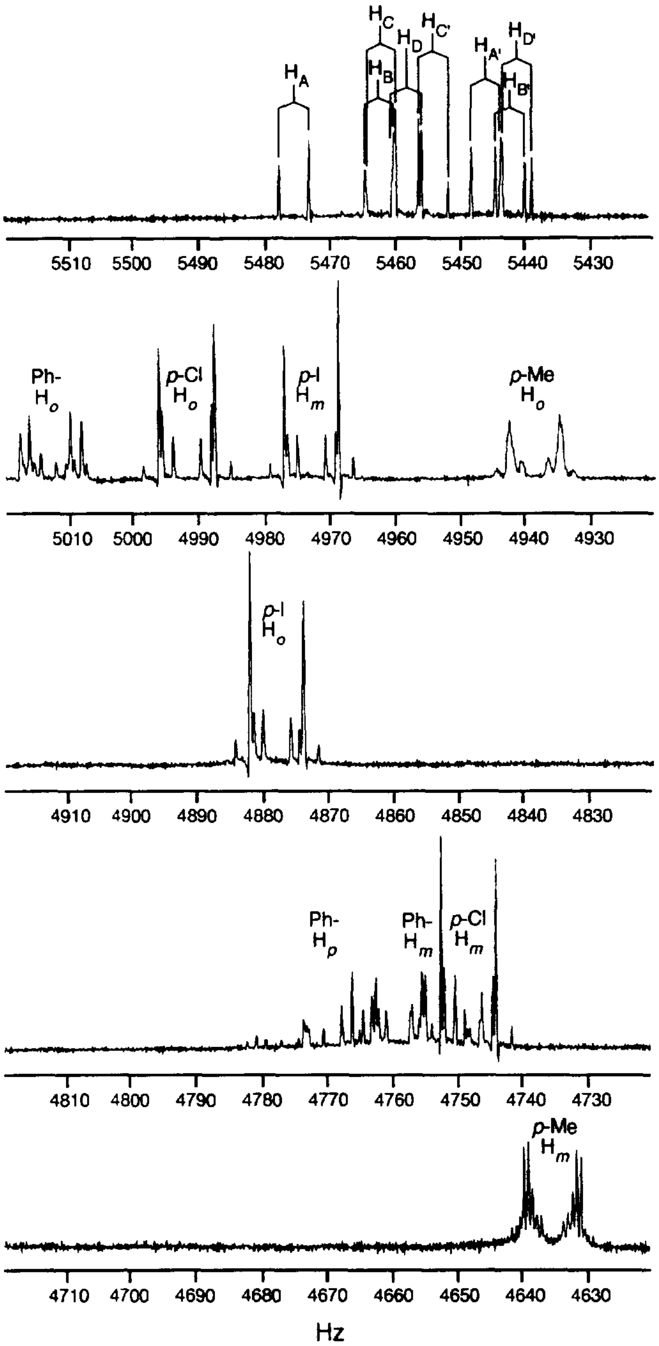


Figure 1. Aromatic region of high resolution ^1H NMR spectrum of **Zn-23** at 620.2 MHz. For lettering of the protons in Figures 1 - 4, see Scheme 7.

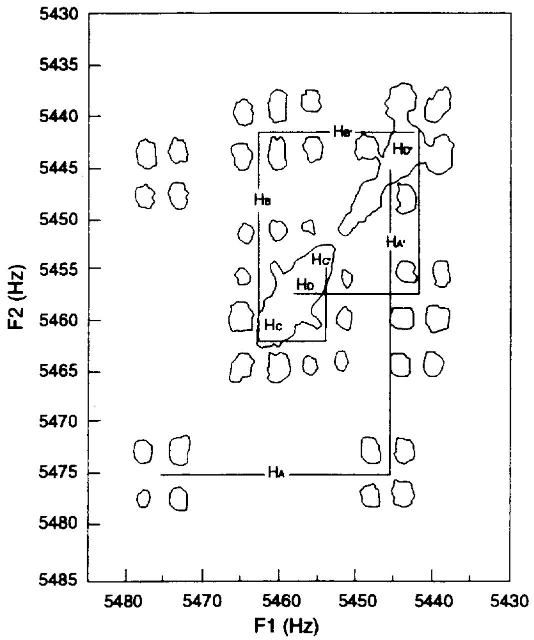


Figure 2. Section of COSY spectrum showing connections in the four pyrrole AB systems.

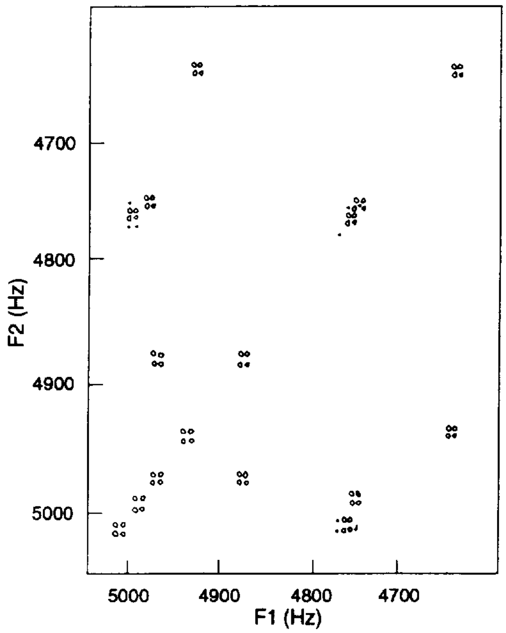


Figure 3. Section of COSY spectrum showing proton connections in the aryl substituents.

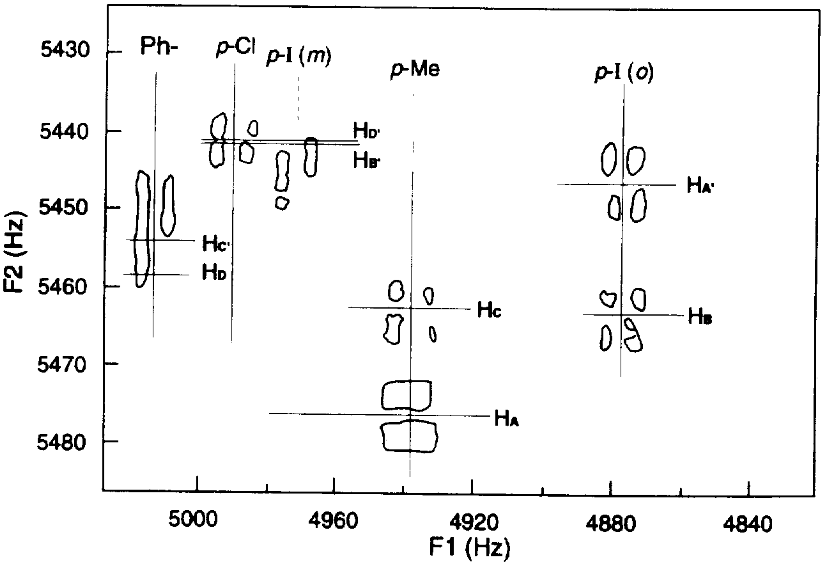


Figure 4. Section of NOESY spectrum showing proximity of *o*-aryl protons to β-pyrrole protons. The effects are small, and some noise and T_1 ridge interference has been whitewashed.

It should be mentioned that the splittings observed are not exactly equal to the isotropic spin-spin coupling constants, since the large magnetic anisotropy of the porphyrin ring causes it to be slightly aligned in the static magnetic field, giving rise to direct dipolar interactions (*D*) which add algebraically to the spin-spin coupling constants (*J*). The effects of dipolar interactions on the porphyrin NMR parameters are significant at high field.[20] In the present case, the direct dipolar couplings (*D*) between pyrrole protons are estimated to be -0.17 Hz, and between H_o and H_m in the aryl groups is estimated as -0.22 Hz.

In a similar high field high resolution ^1H NMR study with free base porphyrin **23**, we found that the proton chemical shifts were within a few hundredths of a Hz of those of the corresponding protons in **Zn-23**. The β-pyrrole proton peaks were unresolved due to the porphyrin NH tautomerism, preventing precise determination of the coupling constants of the β-pyrrole protons. Nonetheless, the close similarity of the spectra of **23** and **Zn-23** made it possible to assign all of the aryl proton peaks (but none of the β-pyrrole proton peaks) in the spectrum of the free base porphyrin based on the assignments of the zinc porphyrin.

With the peak assignments of **23** and **Zn-23** in hand, it was rather straightforward to assign all the aryl proton peaks of **22** and **Zn-22** due to the closely related chemical structures. We found that ^1H NMR spectra collected at 300 MHz were sufficient to assign all of the aryl proton peaks. However, higher field NMR spectroscopy was needed to further resolve the β-pyrrole protons.

The examination of the porphyrins by high field high resolution proton NMR spectroscopy, in conjunction with mass spectral data, clearly indicates that these syntheses have been successfully performed without acidolysis of intermediate dipyrromethanes, and the ABCD-porphyrins are regioisomerically pure.

Deuterium-exchange studies with diacyl-dipyrromethanes:

During the course of various acidolysis experiments we found that upon treatment of **12** with 15 equiv CF_3CO_2D in $CDCl_3$, one set of β-pyrrole proton peaks almost disappeared (Figure 5). The underlying deuterium exchange occurs selectively at H_3 and H_7 (and the pyrrolic NH protons), yielding deuteriated dipyrromethane **26**. The exchange of H_3 and H_7, and not H_2 and H_8, causes the latter to resonate as a distinct singlet (6.96 ppm). Similar results were obtained with **10** in CD_2Cl_2 and with $CDCl_3$ (Scheme 9) but the aromatic region of the spectrum is more complex due to its asymmetric nature.

The unambiguous assignments of the peaks in the ^1H NMR spectra of dipyrromethanes, and thereby the sites of deuterium exchange in acid medium, were identified by NOE difference experiments on the parent dipyrromethane **12**. When **12** was irradiated at the resonance frequency of H_5 (5.63 ppm), a negative NOE response[21] was obtained with peaks at 5.97 ppm and 6.52 ppm. The response from the former was much larger than the latter. This established that the protons giving rise to the peaks at 5.97 ppm are in closer proximity to H_5 than those giving rise to the peaks at 6.52 ppm. The assignments then follow of the multiplet at 5.97 ppm to H_3 and H_7 and of that at 6.52 ppm to H_2 and H_8.

In pyrrole both β-positions are equally reactive toward exchange, but in the dipyrromethane the presence of acyl groups at the 1,9-positions causes exchange to occur exclusively at the 3,7-positions. Exchange regiospecifically at the 3,7-positions can be viewed as involving resonance of the keto-amine and enol-imine canonical forms; the 3,7-positions are γ to the carbonyl and keto-enol tautomerization of α,β-unsaturated carbonyls leads to exchange at the γ-carbon.

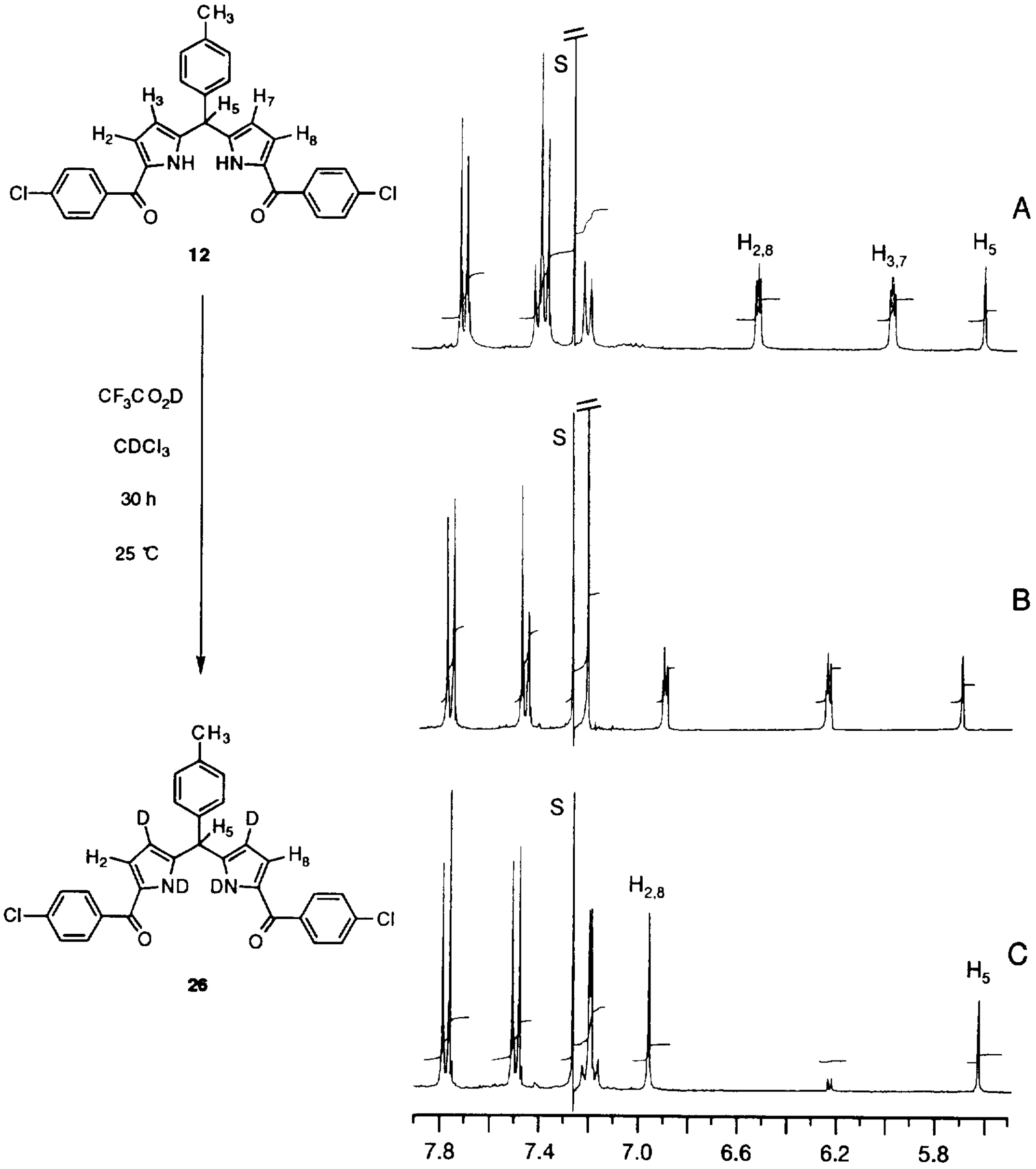
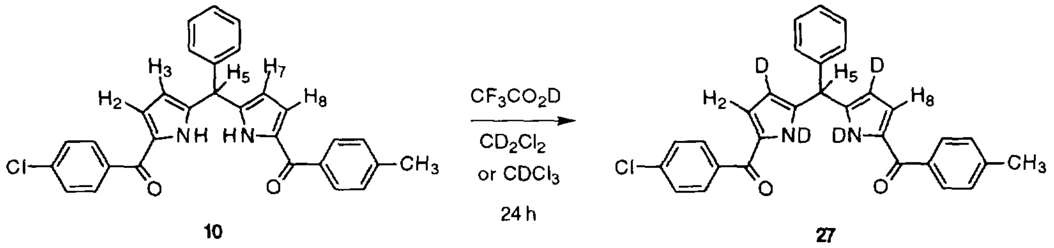


Figure 5. Regiospecific proton exchange measured by ^{1}H NMR spectroscopy in acidic solution (**12** → **26**). **A**: Before adding acid, the 2,8 and 3,7 protons of **12** (0.023 M in $CDCl_3$) give peaks at 6.52 and 5.97 ppm, respectively. **B**: Upon addition of CF_3CO_2D (2.7 equiv), the peaks shift to 6.87 and 6.17 ppm. **C**: After adding more CF_3CO_2D (0.35 M total, 15 equiv) and allowing the solution to stand for 30 h, near total exchange is observed. Note the change in the peaks due to the *p*-tolyl protons (7.19 ppm). The 2,8-protons now appear as a singlet at 6.96 ppm and a very weak peak remains for residual 3,7-protons (6.23 ppm). S = solvent.



Scheme 9. Regiospecific acid-catalyzed exchange in diacyl-dipyrromethanes.

The deuteriated dipyrromethanes can be isolated and re-protonated upon exposure to CF_3CO_2H. These exchange reactions are relatively clean except for the occurrence of a small amount of oxidation. The diacyl-dipyrromethanes are pale yellow in neutral solution, immediately turn pink upon adding acid, and then slowly (over the course of hours) turn light red, a consequence of oxidation yielding the dipyrromethene. However even after 30 h the acidified solution is visually homogeneous and transparent. In the case of **10** → **27**, upon standing in acidified solution a second singlet began to appear 0.05 ppm downfield with intensity 5-10% of that of the dipyrromethane *p*-CH_3 singlet. We attribute this peak to the formation of the dipyrromethene species. No such signal was observed in the conversion of **12** → **26**. Though a small amount of oxidation occurs upon exposure to excess acid for prolonged periods, these experiments illustrate the stability of the 1,9-diacyl-dipyrromethanes to excess acid. This exchange process is amenable to preparative work and should be useful for the synthesis of regiospecifically-deuteriated porphyrins with application in bioorganic studies.

CONCLUSIONS

Routes to porphyrins bearing four different *meso*-substituents have been developed based on the ready availability of dipyrromethanes. The 1- and 9-positions of dipyrromethanes can be functionalized independently by alkylation with benzoxathiolium tetrafluoroborates or with an acylation-alkylation sequence. In many respects functionalization of the free α,α'-positions of the two pyrrole nuclei in dipyrromethanes is more straightforward than is the similar functionalization of the α,α'-positions of pyrrole. These synthetic routes to porphyrins bearing different *meso*-substituents are complementary to the syntheses of naturally-occurring porphyrins. A central issue in the syntheses of naturally-occurring porphyrins involves orientation of the two different β-pyrrole substituents on each pyrrole. Syntheses of porphyrins bearing 4 different *meso*-substituents can be designed with avoidance of the regiochemical problems created by different β-pyrrole substituents.

An attractive synthesis of a regioisomerically pure ABCD-porphyrin involves two one-flask syntheses of *meso*-substituted dipyrromethanes, functionalization of the 1- and 9-positions of one of the dipyrromethanes, and a convergent MacDonald-type 2 + 2 condensation of the two dipyrromethanes. There are three possible regioisomers depending on the sequence of A, B, C, and D groups placed around the porphyrin, and the accessibility of each depends only on substituent compatibilities in the dipyrromethane derivatizations. Refinement of the procedures for acylation, alkylation, and condensation of dipyrromethanes should broaden the scope of this synthesis. The ability to place four different groups around the periphery of the porphyrin should enable syntheses of sophisticated building block porphyrins[22] for application in porphyrin model systems.

EXPERIMENTAL

General. ^{1}H NMR spectra (300 MHz, General Electric GN 300NB and IBM FT-300), IR spectra (Nicolet 5DXB), and absorption spectra (HP 8451A, Cary 3) were collected routinely. Preparative centrifugal TLC was performed with a Harrison Research Chromatotron Model 7924T. Column chromatography was performed on silica (Baker, 200 - 400 mesh). Pyrrole was distilled at atmospheric pressure from CaH_2. CH_2Cl_2 (Fisher, reagent grade) was distilled from K_2CO_3. $CHCl_3$ (Fisher certified A.C.S.) containing 0.75% ethanol was distilled from K_2CO_3. 4-iodobenzaldehyde was obtained from Karl Industries. All other reagents were obtained from Aldrich and used as received unless noted otherwise. The dipyrromethanes and their substituted derivatives are easily visualized upon exposure of thin layer chromatography plates to Br_2 vapor, forming pink or reddish spots.[23] High resolution mass spectra (HRMS) were obtained at the Midwest Center for Mass Spectrometry in Lincoln, Nebraska. Laser desorption mass spectra (LD-MS) were obtained at Argonne National Laboratory. Elemental analyses were obtained at Oneida Laboratories.

The *meso*-dipyrromethanes (**1a-d**) were prepared previously.[6] The benzoxathiolium tetrafluoroborates (**2a-c**) were prepared from *o*-mercaptophenol and the aromatic carboxylic acid according to Method A of Barbero *et al.*[12] This method cleanly affords the desired salts and further purification is not required.

High field high resolution ^{1}H NMR spectroscopy. The spectra were obtained with the porphyrins in a dilute solution (~3 mM) in CS_2, with 0.5% TMS and 0.5% dioxane-d_8 added as reference and lock. The samples were partially degassed and sealed under vacuum. All spectra were obtained using the home-built 620.2 MHz spectrometer at Carnegie Mellon University. 1-D spectra were obtained in the FT mode; typically a spectral width of 1075 Hz was used, with the carrier centered in the aromatic region of the spectrum. 2500 transients of 10720 points were accumulated, the FID was subjected to moderate Lorentzian-Gaussian resolution enhancement, zero-filled to 32768 points, then transformed, phased and plotted using Felix software.

NOE difference spectroscopy. All spectra were collected at 300 MHz with the diacyl-dipyrromethane **12** in $CDCl_3$ containing 0.03% TMS. A spectral width of 5000 Hz was used. 64 transients of 8192 points were acquired when the sample was irradiated at -1.54 ppm (control) and then at 5.63 ppm (NOE). This cycle was repeated 300 times. Then the difference FID (irradiated minus control from each cycle) was Fourier-transformed without resolution enhancement. The difference spectrum was then phased and plotted.

1-[2-(*p*-tolyl)-1,3-benzoxathiolyl]-5-(*p*-bromophenyl)dipyrromethane (3). To a solution of *meso*-(*p*-bromophenyl)dipyrromethane (1.8 g, 6 mmol), pyridine (162 μL, 2 mmol) in 45 mL CH_3CN was added 2-(*p*-tolyl)-1,3-benzoxathiolium tetrafluoroborate (**2a**) (0.629 g, 2 mmol) at once. The deep red solution was stirred for 30 min at room temperature, then diluted with 50 mL ethyl acetate. The mixture was washed with 0.1 N NaOH, water, and dried (Na_2SO_4). TLC analysis (silica, hexanes/ethyl acetate/triethylamine, 80:20:2) showed one minor yellow component (R_f 0.55), two major components consisting of the dialkylated product (R_f 0.51) and the mono-alkylated product (R_f 0.43), and some colored material at the origin. The dark yellow solution was evaporated to dryness and then chromatographed on a silica column (7 x 12 cm, hexanes/ethyl acetate/triethylamine, 80:20:2) that was basified with the eluant before the mixture was loaded. A yellow pigment eluted first. The second band was pale yellow and constituted the dialkylated compound **4**

(0.077 g, 5.1% yield; vide infra). The subsequent yellow band was the desired product (0.71 g, 67%). A slow moving brown fraction was the unreacted starting material. mp 97-98 °C; ^{1}H NMR ($CDCl_3$) δ 8.47 (bs, 1 H, NH), 7.90 (bs, 1 H, NH), 7.51 (AA'BB', 2 H, ArH), 7.42 (AA'BB', 2 H, ArH), 7.13 (AA'BB', 2 H, ArH), 7.08 - 6.98 (m, 4 H, ArH), 6.91 - 6.85 (m, 2 H, ArH), 6.68 - 6.66 (m, 1 H, pyrrole-H), 6.15 - 6.13 (m, 1 H, pyrrole-H), 5.89 - 5.86 (m, 1 H, pyrrole-H), 5.83 - 5.81 (m 1 H, pyrrole-H), 5.69 - 5.66 (m, 1 H, pyrrole-H), 5.35 (s, 1 H, *meso*-H), 2.33 (s, 3 H, CH_3); HRMS ($C_{29}H_{23}N_2BrSO$) calcd mass 526.0714, obsd 526.0722.

1,9-Bis[2-(*p*-tolyl)-1,3-benzoxathiolyl]-5-(*p*-bromophenyl)dipyrromethane (4). Isolated from the previous preparation. mp 84-86 °C; ^{1}H NMR ($CDCl_3$) δ 8.44 (bs, 2 H, NH), 7.51 (AA'BB', 4 H, ArH), 7.41 (AA'BB', 2 H, ArH), 7.13 (AA'BB', 4 H, ArH), 7.07 - 6.99 (m, 6 H, ArH), 6.91 - 6.84 (m, 4 H, ArH), 5.83 - 5.81 (m, 2 H, pyrrole-H), 5.72 - 5.63 (m, 2 H, pyrrole-H), 5.31 (d, 1 H, *meso*-H), 2.34 (s, 6 H, CH_3); HRMS ($C_{43}H_{33}N_2BrS_2O_2$) calcd mass 752.1167, obsd 753.1231.

1-[2-(*p*-tolyl)-1,3-benzoxathiolyl)-5-(*p*-bromophenyl)-9-[2-(*p*-chlorophenyl)-1,3-benzoxathiolyl]-dipyrromethane (5). To a solution of **3** (0.230 g, 0.437 mmol) in 10 mL CH_3CN and pyridine (44 μL, 0.547 mmol) was added 2-(*p*-chlorophenyl)-1,3-benzoxathiolium tetrafluoroborate (**2b**, 0.183 g, 0.547 mmol). The mixture turned brown immediately and was stirred for 20 min at room temperature. 30 mL ethyl acetate was added and the solution was then washed with 0.1 N NaOH, water, and dried (Na_2SO_4). The solvent was evaporated and the resulting dark red residue was chromatographed on a silica column (5 x 12 cm, hexanes/ethyl acetate/triethylamine, 80:20:2) that was basified by washing with the eluant before the mixture was loaded. The desired product was the second yellow pigment (0.34 g, 100%); mp 71-72 °C; ^{1}H NMR ($CDCl_3$) δ 8.52 (bs, 1 H, NH), 8.48 (bs, 1 H, NH), 7.58 (AA'BB', 2 H, ArH), 7.53 (AA'BB', 2 H, ArH), 7.48 - 7.42 (m, 2 H, ArH), 7.29 (AA'BB', 2 H, ArH), 7.15 (AA'BB', 2 H, ArH), 7.08 - 7.02 (m, 6 H, ArH), 6.93 - 6.86 (m, 4 H, ArH), 5.83 - 5.80 (m, 1 H, pyrrole-H), 5.78 - 5.67 (m, 3 H, pyrrole-H), 5.34 (d, 1 H, *meso*-H), 2.35 (s, 3 H, CH_3); HRMS ($C_{42}H_{30}N_2BrClS_2O_2$) calcd mass 772.0621, obsd 773.0671.

1-(*p*-methylbenzoyl)-5-(*p*-bromophenyl)-9-(*p*-chlorobenzoyl)dipyrromethane (6). To a solution of **5** (0.294 g, 0.38 mmol) in 15 mL THF was added Hg(II)O (yellow, 0.082 g, 0.38 mmol) and 48% aq HBF_4 (223 μL, 1.71 mmol). The deep red mixture was stirred at 25 °C for 1.5 h during which Hg(II)O gradually dissolved. The mixture was then diluted with 50 mL ethyl acetate and washed twice with 10% aq KI, 0.1 N NaOH, H_2O and dried (Na_2SO_4). The solvent was evaporated and the resulting red residue was chromatographed on silica (5 x 12 cm, hexanes/ethyl acetate, 80:20:2). After elution of the first three yellow pigments, the eluant was gradually enriched with ~20% ethyl acetate, affording 0.165 g (73%) of a tan solid. mp 138-139 °C; ^{1}H NMR ($CDCl_3$) δ 11.99 (bs, 1 H, NH), 11.96 (bs, 1 H, NH), 7.65-7.60 (m, 4 H, ArH), 7.49 - 7.41 (m, 4 H, ArH), 7.34 (AA'BB', 2 H, ArH), 7.16 (AA'BB', 2 H, ArH), 6.48 - 6.44 (m, 2 H, pyrrole-H), 5.92 - 5.88 (m, 2 H, pyrrole-H), 5.64 (s, 1 H, *meso*-H), 2.36 (s, 3 H, CH_3); HRMS ($C_{30}H_{22}N_2O_2BrCl$) calcd mass 556.0553, obsd 557.0557. Anal. calcd: C, 64.74; H, 3.99; N, 5.04. Found: C, 64.08; H, 4.34; N, 4.81.

1-[2-(*p*-tolyl)-1,3-benzoxathiolyl]-5-phenyldipyrromethane (7). To a solution of 1.8 g of *meso*-phenyldipyrromethane (**1b**, 8.1 mmol) in 62 mL CH_3CN and pyridine (218 μL, 2.7 mmol) was added 2-(*p*-

tolyl)-1,3-benzoxathiolium tetrafluoroborate (0.849 g, 2.7 mmol). The dark red mixture was worked up after 20 min in the same manner as for **3**. A yellow pigment eluted first followed by the bright yellow dialkylated compound **8** (0.176 g, 10%; vide infra). The desired product eluted as the third band from the column yielding a bright yellow solid (0.66 g, 55%). A slow moving brownish band consisted of the unreacted starting material. mp 62-65 °C; ^{1}H NMR ($CDCl_3$) δ 8.46 (s, 1 H, NH), 7.89 (s, 1 H, NH), 7.51 (AA'BB', 2 H, ArH), 7.32 - 7.18 (m, 5 H, ArH), 7.12 (AA'BB', 2 H, ArH), 7.05 - 6.98 (m, 2 H, ArH), 6.91 - 6.82 (m, 2 H, ArH), 6.68 - 6.66 (m, 1 H, pyrrole-H), 6.15 - 6.13 (m, 1 H, pyrrole-H), 5.91 - 5.90 (m, 1 H, pyrrole-H), 5.83 - 5.81 (m, 1 H, pyrrole-H), 5.72 - 5.69 (m, 1 H, pyrrole-H), 5.41 (s, 1 H, *meso*-H), 2.33 (s, 3 H, CH_3); HRMS ($C_{29}H_{24}N_2SO$) calcd mass 448.1609, obsd 448.1600.

1,9-Bis[2-(*p*-tolyl)-1,3-benzoxathiolyl]-5-phenyldipyrromethane (8). Isolated from the previous preparation. mp 75 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 8.43 (bs, 2 H, NH), 7.50 (AA'BB', 4 H, ArH), 7.30 - 7.25 (m, 3 H, ArH), 7.19 - 7.16 (m, 2 H, ArH), 7.11 (AA'BB', 4 H, ArH), 7.05 - 6.96 (m, 4 H, ArH), 6.89 - 6.82 (m, 4 H, ArH), 5.82 - 5.81 (m, 2 H, pyrrole-H), 5.75 - 5.64 (m, 2 H, pyrrole-H), 5.35 (d, 1 H, *meso*-H), 2.31 (s, 6 H, CH_3); HRMS ($C_{43}H_{34}N_2S_2O_2$) calcd mass 674.8752, obsd 675.2115 (M+H), 674.2048.

1-[2-(*p*-tolyl)-1,3-benzoxathiolyl]-5-phenyl-9-[2-(*p*-chlorophenyl)-1,3-benzoxathiolyl]-dipyrromethane (9). To a solution of **7** (0.54 g, 1.21 mmol) in 27.5 mL acetonitrile and pyridine (122 µL, 1.51 mmol) was added 2-(*p*-chlorophenyl)-1,3-benzoxathiolium tetrafluoroborate (**2b**, 0.504 g, 1.51 mmol). The mixture turned brown immediately and was stirred for 20 min at room temperature. 60 mL ethyl acetate was added and the solution was then washed with 0.1 N NaOH, water, and dried (Na_2SO_4). The solvent was evaporated to dryness and the resulting dark brown residue was chromatographed on a silica column (5 x 12 cm, hexanes/ethyl acetate/triethylamine, 80:20:2) that was basified with the solvent before the mixture was loaded. The desired product was the second yellow pigment (0.82 g, 98%). mp 75 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 8.48 (bs, 1 H, NH), 8.44 (bs, 1 H, NH), 7.56 (AA'BB', 2 H, ArH), 7.50 (AA'BB', 2 H, ArH), 7.32 - 7.23 (m, 5 H, ArH), 7.17 (AA'BB', 2 H, ArH), 7.11 (AA'BB', 2 H, ArH), 7.04 - 6.97 (m, 4 H, ArH), 6.89 - 6.84 (m, 4 H, ArH), 5.82 - 5.81 (m, 1 H, pyrrole-H), 5.75 - 5.66 (m, 3 H, pyrrole-H), 5.35 (s, 1 H, *meso*-H), 2.31 (s, 3 H, CH_3); LD-MS ($C_{42}H_{31}ClN_2S_2O_2$) calcd avg mass 695.3, obsd 694.6.

1-(*p*-methylbenzoyl)-5-phenyl-9-(*p*-chlorobenzoyl)dipyrromethane (10). To a solution of **9** (0.30 g, 0.432 mmol) in 17 mL THF was added Hg(II)O (yellow, 0.096 g, 0.432 mmol) and 48% aq HBF_4 (254 µL, 1.94 mmol). The deep red solution was treated identically as for **6** after 1.5 h. The dark brown residue was chromatographed on silica (5 x 12 cm, hexanes/ethyl acetate/triethylamine, 80:20:2). After the elution of the first three yellow pigments, the solvent was gradually enriched with ethyl acetate (~20% of the solvent volume) to elute the desired product, affording 0.166 g (80%) of a tan solid. mp 95-98 °C; ^{1}H NMR ($CDCl_3$) δ 12.0 (bs, 1 H, NH), 11.9 (bs, 1 H, NH), 7.69 - 7.64 (m, 4 H, ArH), 7.57 (AA'BB', 2 H, ArH), 7.40 - 7.31 (m, 5 H, ArH), 7.17 (AA'BB', 2 H, ArH), 6.48 - 6.44 (m, 2 H, pyrrole-H), 5.93 - 5.91 (m, 2 H, pyrrole-H), 5.69 (s, 1 H, *meso*-H), 2.36 (s, 3 H, CH_3); HRMS ($C_{30}H_{23}ClN_2O_2$) calcd mass 478.1448, obsd 478.1463. Anal. calcd: C, 75.29; H, 4.85; N, 5.86. Found: C, 74.71; H, 5.64; N, 5.70.

1-(*p*-chlorobenzoyl)-5-(*p*-tolyl)dipyrromethane (11). To a solution of ethyl magnesium bromide (1.0 M THF solution, 12.1 mL) was added a solution of *meso*-(*p*-tolyl)dipyrromethane **1c** (1.2 g, 5.08 mmol) in 10 mL THF over a period of 5 min. The mixture was stirred for 30 min at room temperature then a solution of *p*-chlorobenzoyl chloride (1.78 g, 10.16 mmol) in 10 mL THF was added dropwise. The dark orange solution was stirred an additional 3 h and then diluted with 100 mL CH_2Cl_2. The mixture was washed with 100 mL sat NH_4Cl, H_2O and dried (Na_2SO_4). The solvent was evaporated to dryness and the resulting brown solid was chromatographed on silica (8 x 20 cm, CH_2Cl_2/ethyl acetate, 50:1). A yellow impurity eluted first followed by a tan band which was identified as the mono-acylated product (0.47 g, 24% yield). The diacylated product **12** eluted (CH_2Cl_2/ethyl acetate, 10:1) as a slow moving slightly-pink band (0.62 g, 24%; vide infra). mp 74-75 °C; ^{1}H NMR ($CDCl_3$) δ 9.49 (s, 1 H, NH), 8.00 (s, 1 H, NH), 7.58 (AA'BB', 2 H, Ar(*p*-Cl)-H), 7.41 (AA'BB, 2 H, Ar(tolyl)-H), 7.13 - 7.06 (m, 4 H, ArH), 6.77 - 6.75 (m, 1 H, pyrrole-H), 6.68 - 6.67 (m, 1 H, pyrrole-H), 6.17 - 6.13 (m, 1 H, pyrrole-H), 6.09 - 6.06 (m, 1 H, pyrrole-H), 5.98 - 5.96 (m, 1 H, pyrrole-H), 5.49 (s, 1 H, *meso*-H), 2.32 (s, 3 H, CH); HRMS ($C_{23}H_{19}N_2OCl$) calcd mass 374.1186, obsd 374.1188; LD-MS obsd 374.8. Anal. calcd: C, 73.26; H, 5.02; N, 7.30. Found: C, 73.72; H, 5.43; N, 6.98.

1,9-bis(*p*-chlorobenzoyl)-5-(*p*-tolyl)dipyrromethane (12). Isolated from the previous preparation. mp 115-117 °C; ^{1}H NMR ($CDCl_3$) δ 11.46 (bs, 2 H, NH), 7.69 (AA'BB', 4 H, ArH), 7.41 - 7.35 (m, 6 H, ArH), 7.19 (AA'BB', 2 H, ArH), 6.53 - 6.51 (m, 2 H, pyrrole-H), 5.98 - 5.96 (m, 2 H, pyrrole-H), 5.63 (s, 1 H, *meso*-H), 2.37 (s, 3 H, CH_3); HRMS ($C_{30}H_{22}N_2Cl_2O_2$) calcd mass 513.1058, obsd 512.1049; LD-MS obsd 514.3. Anal. calcd: C, 70.18; H, 4.32; N, 5.46. Found: C, 70.04; H, 4.67; N, 4.98.

1-(*p*-methylbenzoyl)-5-phenyldipyrromethane (13) A solution of ethyl magnesium bromide (1 M solution in THF, 20 mL, 20 mmol) was added dropwise to a solution of *meso*-phenyldipyrromethane **1b** (2.0 g, 9 mmol) in 10 mL THF under an argon atmosphere. The reaction is exothermic and gas evolution is immediately observed. The dark brown solution was stirred for 30 min then a solution of *p*-toluoyl chloride (1.69 mL, 12.6 mmol) in 10 mL THF was added dropwise. The mixture was stirred an additional 2 h then the reaction was quenched by adding 50 mL sat NH_4Cl. The mixture was combined with 100 mL CH_2Cl_2. The organic layer was washed with water and dried (Na_2SO_4). The solvent was evaporated and the resulting black solid was flash-chromatographed (silica, 8 x 20 cm, CH_2Cl_2/ethyl acetate, 25:1). Unreacted dipyrromethane eluted first followed by the desired product as a slow moving yellow band (1.92 g, 63%). The last mobile band was identified as the diacyl-dipyrromethane, yielding 0.80 g (**14**, 19%; vide infra). Analytically pure compound was obtained by repeated column chromatography on silica with CH_2Cl_2. mp 70-72 °C; ^{1}H NMR($CDCl_3$) δ 10.02 (s, 1 H, NH), 8.34 (s, 1 H, NH), 7.70 (AA'BB', 2 H, Ar(tolyl)-H), 7.30 - 7.17 (m, 7 H, ArH), 6.80 - 6.78 (m, 1 H, pyrrole-H), 6.65 - 6.62 (m, 1 H, pyrrole-H), 6.15 - 6.12 (m, 1 H, pyrrole-H), 6.09 - 6.07 (m, 1 H, pyrrole-H), 5.99 - 5.98 (m, 1 H, pyrrole-H), 5.55 (s, 1 H, *meso*-H), 2.41 (s, 3 H, CH_3); HRMS ($C_{23}H_{20}N_2O$) calcd mass 340.1576, obsd 340.1580; LD-MS obsd 340.7. Anal. calcd: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.06; H, 6.35; N, 7.97.

1,9-Bis-(*p*-methylbenzoyl)-5-phenyldipyrromethane (14). Isolated from the previous preparation. mp 75-76 °C; ^{1}H NMR ($CDCl_3$) δ 11.06 (bs, 2 H, NH), 7.69 (AA'BB', 4 H, ArH), 7.49 - 7.45 (m, 2 H, ArH), 7.40 - 7.30 (m, 3 H, ArH), 7.19 (AA'BB', 4 H, ArH), 6.57 (m, 2 H, pyrrole-H), 5.97 - 5.94 (m, 2 H, pyrrole-H), 5.63 (s, 1 H, *meso*-H), 2.38 (s, 6 H, CH_3); HRMS ($C_{31}H_{26}N_2O_2$) calcd mass 458.1994, obsd 458.2011; LD-MS obsd 458.7. Anal. calcd for $C_{31}H_{26}N_2O_2 \cdot 0.1EtOAc$: C, 80.69; H, 5.78; N, 5.99. Found: C 80.17, H 6.03, N 5.67.

1-(*p*-methylbenzoyl)-5-phenyl-9-[2-(*p*-chlorophenyl)-1,3-benzoxathiolyl]dipyrromethane (15). To a solution of **13** (2.0 g, 5.88 mmol) in 25 mL acetonitrile and pyridine (0.48 mL, 5.88 mmol) was added dropwise a solution of 2-(*p*-chlorophenyl)-1,3-benzoxathiolium tetrafluoroborate (1.96 g, 5.88 mmol) in 25 mL acetonitrile under argon. The mixture was stirred for 30 min at room temperature then was combined with 100 mL CH_2Cl_2. The organic layer was washed with 0.1 N NaOH, water, and dried (Na_2SO_4). The residue obtained after evaporation of the solvent was chromatographed on silica (8 x 25 cm, CH_2Cl_2/ethyl acetate/triethylamine, 50:2:0.5). A yellow impurity eluted first followed by a red band which was the desired product. Yield 3.38 g (98%). mp 94-97 °C; IR (KBr) 1604 cm^{-1}, s; ^1H NMR ($CDCl_3$) δ 9.28 (bs, 1 H, NH), 8.49 (bs, 1 H, NH), 7.73 (AA'BB', 2 H, ArH), 7.57 (AA'BB', 2 H, ArH), 7.35 - 7.19 (m, 9 H, ArH), 7.04 - 6.98 (m, 2 H, Ar(benzoxathiolyl)-H), 6.89 - 6.85 (m, 2 H, Ar(benzoxathiolyl)-H), 6.79 - 6.77 (m, 1 H, pyrrole-H),6.05 - 6.02 (m, 1 H, pyrrole-H), 5.78 - 5.75 (m, 2 H, pyrrole-H), 5.47 (s, 1 H, *meso*-H), 2.40 (s, 3 H, CH_3); LD-MS ($C_{36}H_{27}N_2O_2ClS$) calcd avg mass 587.1; obsd 586.7.

15 → 10. To a suspension of **15** (0.63 g, 1.07 mmol) and Hg(II)O (yellow, 0.23 g, 1.06 mmol) in 30 mL THF was added HBF_4 (48% aq, 0.2 mL, 1.1 mmol). The mixture was stirred for 1 h at room temperature, then combined with 50 mL CH_2Cl_2. The mixture was washed successively with 10% aq KI, 0.1 N NaOH, water, and dried (Na_2SO_4). The solvent was evaporated to dryness and the resulting dark brown solid was chromatographed on silica (4 x 20 cm). A small amount of impurity bands eluted first (5% ethyl acetate in CH_2Cl_2) then elution with ethyl acetate/CH_2Cl_2 (1/1) gave pure product as a yellow band. Yield 0.48 g (93%). All spectral characteristics were identical with **10** prepared in the route from **9**.

2-(4-methoxybenzoyl)-5-[2-(4-methoxyphenyl)-1,3-benzoxathiolyl]pyrrole (17). A solution of 35% aq HBF_4 (0.9 mL) was added dropwise to the suspension of 2,5-bis[2-(4-methoxyphenyl)-1,3-benzoxathiolyl]pyrrole (**16**, 1 g, 1.81 mmol)[11] and Hg(II)O (yellow, 196.3 mg, 0.91 mmol) in 10 mL THF. The mixture was stirred at room temperature until dissolution occurred and then stirring was continued for three min. Then the reaction mixture was extracted with CH_2Cl_2 (2 x 100 mL). The extracts were washed with 10% aq KI (2 x 75 mL), 5% NaOH (100 mL), and H_2O (200 mL), dried (Na_2SO_4), and evaporated. The products (silica TLC, CH_2Cl_2) consisted of unreacted starting material (R_f 0.88), mono-acyl product (R_f 0.45), and di-acyl product (R_f 0.16). Chromatography on a silica gel column with CH_2Cl_2/hexanes (1:1) gave the product as a white solid (710 mg, 89%). (In addition unreacted starting material was recovered in 7% yield and the diacyl-dipyrromethane was isolated in 3% yield.) mp 66-69 °C; ^1H NMR ($CDCl_3$) δ 9.90 (bs, 1 H, NH), 7.90 (AA'BB', 2 H, ArH), 7.56 (AA'BB', 2 H, ArH), 7.20 - 6.90 (m, 6 H, ArH), 6.88 (AA'BB', 2 H, ArH), 6.75 (m, 1 H, pyrrole-H), 6.27 (m, 1 H, pyrrole-H), 3.90 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3); HRMS ($C_{26}H_{21}O_4SN$) calcd mass 443.5170, obsd 443.1196. Anal. calcd: C, 70.41; H, 4.77; N, 3.16. Found: C, 70.53; H, 4.68; N, 3.26.

2-[α-Hydroxy-4-methoxybenzyl]-5-[2-(4-methoxyphenyl)-1,3-benzoxathiolyl]-pyrrole (18). Four portions of $NaBH_4$ (85 mg each, 2.26 mmol, 9.02 mmol total) were added at 15 min intervals to a solution of **17** (400 mg, 0.902 mmol) in 7 mL CH_3OH and 3 mL CH_2Cl_2, and the mixture was stirred at room temperature for 30 min. Then 100 mL of CH_2Cl_2 was added and the mixture was washed with 10% Na_2CO_3 (50 mL). After evaporation of the solvent, the product was obtained in 93% yield as a white solid from CH_2Cl_2/hexanes. mp 125-127 °C; ^1H NMR ($CDCl_3$) δ 8.85 (bs, 1 H, NH), 7.54 (m, 2 H, ArH), 7.32 (m, 2 H, ArH), 7.12 - 6.99 (m, 2 H, ArH), 6.96 - 6.82 (m, 6 H, ArH), 5.83 - 5.75 (m, 3 H, pyrrole-H and CH), 3.82 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 2.22 (bm, 1 H, OH); HRMS ($C_{26}H_{23}O_4SN$) calcd 445.5329, obsd 427.1240 (M-H_2O). Anal. calcd for $C_{26}H_{23}O_4SN \cdot 1/4CH_2Cl_2$: C, 67.55; H, 5.07; N, 3.00. Found: C, 67.93; H, 5.16; N, 3.13.

1-[2-(*p*-tolyl)-1,3-benzoxathiolyl]-5-(*p*-methoxyphenyl)-9-[2-(*p*-methoxyphenyl)-1,3-benzoxathiolyl]dipyrromethane (20). TFA (3.5 μL, 0.045 mmol) was added to a mixture of **18** (200 mg, 0.45 mmol) and 2-[2-(*p*-tolyl)-1,3-benzoxathiolyl]pyrrole (**19**, 158 mg, 0.54 mmol; prepared by alkylation of pyrrole[11] with 2-(*p*-tolyl)-1,3-benzoxathiolium tetrafluoroborate) in 45 mL CH_2Cl_2 at 0 °C. The dark red solution was stirred at 0 °C for 1 h. Then 10 μL triethylamine was added to the reaction mixture and the solvent was evaporated. The crude residue was chromatographed on a silica gel Chromatotron rotor with hexanes/CH_2Cl_2/triethylamine (80:10:1) yielding the desired product (172 mg, 53%). mp 107-110 °C; ^1H NMR ($CDCl_3$) δ 8.50 (bs, 2 H, NH), 7.65 - 7.52 (m, 4 H, ArH), 7.23 - 6.81 (m, 16 H, ArH), 5.87 (m, 2 H, pyrrole-H), 5.75 (m, 2 H, pyrrole-H), 5.37 (s, 1 H, *meso*-H), 3.84 (s, 6 H, $ArOCH_3$), 2.37 (s, 3 H, CH_3). Anal. calcd for $C_{44}H_{36}O_4S_2N_2$: C, 73.31; H, 5.03; 3.89. Found: C, 73.75; H, 5.59; N, 3.66.

1-(*p*-methylbenzoyl)-5-(*p*-methoxyphenyl)-9-(*p*-methoxybenzoyl)dipyrromethane (21). 35% aq HBF_4 (263 μL, 0.78 mmol) was added to the yellow suspension of **20** (250 mg, 0.35 mmol) and Hg(II)O (yellow, 76 mg, 0.35 mmol) in 8 mL THF. The mixture was stirred at room temperature for 1 h. Then the reaction mixture was extracted with CH_2Cl_2 (2 x 50 mL). The extract was washed with 10% KI (2 x 50 mL), 5% NaOH (50 mL), and H_2O (50 mL), dried (Na_2SO_4), and evaporated. TLC analysis (silica, hexanes/ethyl acetate 2:1) showed the major product (R_f 0.2). The residue was chromatographed on a silica gel Chromatotron rotor with hexanes/ethyl acetate (4:1) to give the product as a pink-tinted solid (160 mg, 92%). mp 120-121 °C; ^1H NMR ($CDCl_3$) δ 11.15 (bs, 2 H, NH), 7.81 (AA'BB', 2 H, ArH), 7.70 (AA'BB', 2 H, ArH), 7.43 (AA'BB', 2 H, ArH), 7.21 (AA'BB', 2 H, ArH), 6.93 - 6.91 (AA'BB', 4 H, ArH), 6.57 (m, 2 H, pyrrole-H), 5.98 (m, 2 H, pyrrole-H), 5.61 (s, 1 H, *meso*-H), 3.86 (s, 3 H, $ArOCH_3$), 3.83 (s, 3 H, $ArOCH_3$), 2.41 (s, 3 H, CH_3). Anal. calcd for $C_{32}H_{28}O_4N_2$: C, 76.17; H, 5.59, N 5.55. Found: C, 75.80; H, 5.88; N, 5.37.

5-(*p*-chlorophenyl)-10-(*p*-bromophenyl)-15-(*p*-tolyl)-20-(*p*-iodophenyl)porphyrin (22). To a solution of **6** (0.09 g, 0.162 mmol) in 7 mL THF/ethanol (1:1) was added $NaBH_4$ (0.102 g, 2.7 mmol). The slightly brown reaction mixture was stirred for 1 h at room temperature and turned pale yellow. The reaction was monitored by IR (disappearance of the carbonyl stretch at ~1600 cm^{-1} and appearance of a hydroxy stretch at ~3340 cm^{-1}) and by TLC (silica, hexanes/ethyl acetate/triethylamine, 66:33:2); the latter showed complete conversion to the diol (diacyl-dipyrromethane R_f ~0.7, dipyrromethane-diol R_f ~0.3) with no observable side products. Then the mixture was diluted with 40 mL ethyl acetate and washed with 0.1 N NaOH until gas evolution ceased. The organic layer was then washed with water, dried (Na_2SO_4), and evaporation of the solvent and vacuum drying afforded the bright yellow **6-diol** (0.090 g, 100%). ^1H NMR ($CDCl_3$) δ 10.12 (bs, 1 H, NH), 10.08 (bs, 1 H, NH), 7.35 - 7.22 (m, 8 H, ArH), 7.17 - 7.10 (m, 5 H, ArH), 5.79 - 5.69 (m, 4 H, pyrrole-H), 5.44-5.29 (m, 3 H, *meso*-H and benzylic-H), 2.33 (s, 3 H, CH_3). To a solution of **6-diol** (0.090 g, 0.161 mmol) and *meso*-(*p*-iodophenyl)dipyrromethane **1d** (0.056 g, 0.161 mmol) in 16 mL $CHCl_3$ was added trifluoroacetic acid (69.5 μL, 0.902 mmol, 5.6 equiv). The solution was stirred for 20 min at room temperature then 1 mL triethylamine and DDQ (0.183 g, 5 equiv) were added. The mixture was stirred for 1 h and then the solvent was evaporated to dryness. The remaining black residue was flash-chromatographed on silica (4 x 12 cm, hexanes/CH_2Cl_2 1:1), affording the desired product as a fast moving deep purple band (18 mg, 14%). ^1H NMR (CS_2) δ 8.75 - 8.69 (m, 8 H, pyrrole-H), 8.03 (m, 2 H, *p*-chlorophenyl(*o*)-H), 7.99 (m, 2 H, *p*-bromophenyl(*o*)-H), 7.97 (m, 2 H, *p*-iodophenyl(*m*)-H), 7.95 (m, 2 H, *p*-tolyl(*o*)-H), 7.84 (m, 2 H, *p*-iodophenyl(*o*)-H), 7.78 (m, 2 H, *p*-bromophenyl(*m*)-H), 7.63 (m, 2 H, *p*-chlorophenyl(*m*)-H), 7.45 (m, 2 H, *p*-tolyl(*o*)-H), 2.66 (m, 3 H, CH_3), -3.03 (s, 2 H, NH); LD-MS ($C_{45}H_{29}N_4BrClI$) calcd avg mass 868.0, obsd 868.1; λ_{abs} (log ε) in toluene, 421 (5.56, fwhm 13.5 nm), 515 (4.23), 550 (3.93), 595 (3.71), 648 (3.63).

Zn(II)-5-(*p*-chlorophenyl)-10-(*p*-bromophenyl)-15-(*p*-tolyl)-20-(*p*-iodophenyl)porphyrin (Zn-22). A sample of **22** (5 mg, 5.7 μmol) was dissolved in 5 mL $CHCl_3$, then a methanolic solution of $Zn(OAc)_2 \cdot 2H_2O$ (14 mg, 0.06 mmol, 1 mL methanol) was added. The reaction mixture was stirred at room temperature and was monitored by fluorescence excitation spectroscopy. After stirring overnight at room temperature the reaction mixture was washed with 10% $NaHCO_3$, water, dried (Na_2SO_4), filtered, and concentrated affording 5 mg (100%) of **Zn-22** as a purple solid. ^1H NMR (CS_2) δ 8.85 - 8.78 (m, 8 H, pyrrole-H), 8.05 (m, 2 H, *p*-chlorophenyl(*o*)-H), 8.02 (m, 2 H, *p*-bromophenyl(*o*)-H), 7.99 (m, 2 H, *p*-iodophenyl(*m*)-H), 7.96 (m, 2 H, *p*-tolyl(*o*)-H), 7.86 (m, 2 H, *p*-iodophenyl(*o*)-H), 7.82 (m, 2 H, *p*-bromophenyl(*m*)-H), 7.66 (m, 2 H, *p*-chlorophenyl(*m*)-H), 7.48 (m, 2 H, *p*-tolyl(*o*)-H), 2.69 (m, 3 H, CH_3). LD-MS ($C_{45}H_{27}N_4BrClIZn$) calcd avg mass 931.4, obsd 1737.2 (2M - I + H), 1656.6 (2M - I - Br + H), 931.2 (M, most intense), 852.3 (M - Br + H); λ_{abs} (toluene) 424, 551 nm.

5-(*p*-chlorophenyl)-10-phenyl-15-(*p*-tolyl)-20-(*p*-iodophenyl)porphyrin (23). To a solution of **10** (0.200 g, 0.418 mmol) in 20 mL THF/ethanol (1:1) was added $NaBH_4$ (0.264 g, 7 mmol). The slightly brown reaction mixture was stirred for 1 h at room temperature. TLC analysis (silica, hexanes/ethyl acetate/triethylamine, 66:33:2) showed complete conversion to the diol (diacyl-dipyrromethane R_f ~0.7, dipyrromethane-diol R_f ~0.3) with no observable side products. The resulting pale yellow mixture was diluted with 70 mL ethyl acetate and washed with 0.1 N NaOH until gas evolution ceased. The organic layer was then washed with water twice and dried (Na_2SO_4). The bright yellow **10-diol** solid obtained after evaporation of the solvent and vacuum drying (0.2 g, 100%) showed in the IR spectrum the alcohol stretch (KBr, 3337 cm^{-1}, s) and the absence of the carbonyl group. A portion of the **10-diol** material (0.048 mg, 0.1 mmol) and *meso*-(*p*-iodophenyl)dipyrromethane **1d** (0.035 g, 0.1 mmol) were dissolved in 10 mL $CHCl_3$ and trifluoroacetic acid (43 μL, 0.56 mmol, 5.6 equiv) was injected. The solution was stirred for 20 min and then 1 mL triethylamine and DDQ (0.114 g, 5 equiv) were added and stirring was continued for another 1 h. The solvent was evaporated to dryness and the resulting black residue was chromatographed on silica (4 x 12 cm, hexanes/CH_2Cl_2 1:1). The porphyrin eluted first, affording 0.010 g (13%) of a purple solid. ^1H NMR 620.2 MHz (CS_2) δ 8.749 (m, 8 H, pyrrole-H), 8.122 (m, 2 H, phenyl(*o*)-H), 8.085 (m, 2 H, *p*-chlorophenyl(*o*)-H), 8.041 (m, 2 H, *p*-iodophenyl(*m*)-H), 8.003 (m, 2 H, *p*-tolyl(*o*)-H), 7.897 (m, 2 H, *p*-iodophenyl(*o*)-H), 7.680 (m, 5 H, phenyl(*p*)-H, phenyl(*m*)-H and *p*-chlorophenyl(*m*)-H), 7.497 (m, 2 H, *p*-tolyl(*m*)-H), 2.689 (m, 3 H, CH_3), -2.973 (bs, 2 H, NH); LD-MS ($C_{45}H_{30}N_4ClI$) calcd avg mass 789.1, obsd 788.8; λ_{abs} (log ε) in toluene, 421 (5.56, fwhm 13.5 nm), 515 (4.24), 550 (3.93), 595 (3.71), 648 (3.58).

Zn(II)-5-(*p*-chlorophenyl)-10-phenyl-15-(*p*-tolyl)-20-(*p*-iodophenyl)porphyrin (Zn-23). To a solution of **23** (5 mg, 6.3 μmol) in 5 mL $CHCl_3$ was added a solution of $Zn(OAc)_2 \cdot 2H_2O$ (14 mg, 0.06 mmol, 1 mL methanol). The reaction mixture was stirred at room temperature and was monitored by fluorescence excitation spectroscopy. After stirring at room temperature overnight the reaction mixture was washed with 10% $NaHCO_3$, water, dried (Na_2SO_4), filtered, and concentrated affording 5 mg (100%) of **Zn-23** as a purple solid. ^1H NMR 620.2 MHz (CS_2) δ 8.829 (d, 1H, pyrrole-H_C, 4.52 Hz), 8.808 (d, 1H, pyrrole-H_B, 4.52 Hz), 8.807 (d, 1H, pyrrole-H_A, 4.52 Hz), 8.800 (d, 1H, pyrrole-H_D, 4.50 Hz), 8.794 (d, 1H, pyrrole-$H_{A'}$, 4.52 Hz), 8.782 (d, 1H, pyrrole-$H_{C'}$, 4.54 Hz), 8.773 (d, 1H, pyrrole-$H_{D'}$, 4.50 Hz), 8.772 (d, 1H, pyrrole-$H_{B'}$, 4.52 Hz), 8.083 (m, 2 H, phenyl(*o*)-H, *om* 7.23 Hz, *op* 1.73 Hz, *oo'* 1.90 Hz, *om'* 0.63 Hz), 8.049 (m, 2 H, *p*-chlorophenyl(*o*)-H, *om* 7.99 Hz), 8.018 (m, 2 H, *p*-iodophenyl(*m*)-H, *om* 7.62 Hz), 7.964 (m, 2 H, *p*-tolyl(*o*)-H, *om* 7.72 Hz), 7.867 (m, 2 H, *p*-iodophenyl(*o*)-H, *om* 7.62 Hz), 7.691 (m, 1 H, phenyl(*p*)-H, *po* 1.73 Hz, *pm* 8.04 Hz), 7.667 (m, 2 H, phenyl(*m*)-H, *mp* 8.04 Hz, *mo* 7.23 Hz, *mm'* 1.48 Hz, *mo'* 0.63 Hz), 7.656 (m, 2 H, *p*-chlorophenyl(*m*)-H, *om* 7.99 Hz), 7.473 (m, 2 H, *p*-tolyl(*m*)-H, *om* 7.72 Hz), 2.658 (m, 3 H, CH_3); LD-MS ($C_{45}H_{28}N_4ClIZn$) calcd avg mass 852.5, obsd 852.3; λ_{abs} (toluene) 424, 551 nm.

Acid-catalyzed porphyrin formation from *meso*-(*p*-iodophenyl)dipyrromethane. Compound **1d** (6.9 mg, 0.02 mmol) was dissolved in 2 mL $CHCl_3$ in a one dram snap top vial. Various amounts of 2.5 M $BF_3 \cdot O(Et)_2$ (2.7 μL or 5.3 μL) or TFA (1.6 μL, 5.1 μL, 8.6 μL or 17.3 μL) were injected into the solution via a gas-tight syringe. The solution was stirred at room temperature. Then 10 μL of the reaction mixture was removed and oxidized with 150 μL DDQ solution (toluene, 10 mM) and diluted with 3 mL CH_2Cl_2/ethanol (3:1). Absorption spectra of the diluted solution were taken and porphyrin yield was assessed photometrically assuming $\varepsilon_{420} = 500{,}000\ M^{-1}cm^{-1}$.

Acid-catalyzed reaction of 6-diol and 10-diol. In a one dram snap top vial **6-diol** (5.6 mg, 0.01 mmol) or **10-diol** (4.8 mg, 0.01 mmol) was dissolved in 1 mL $CHCl_3$, then $BF_3 \cdot O(Et)_2$ (2.5 M in $CHCl_3$, 3.3 μL, 0.00825 mmol) or TFA (2.6 μL, 4.3 μL or 8.6 μL) was injected via a gas-tight syringe. The solution was stirred at room temperature. Then 10 μL of the reaction mixture was removed and oxidized with 150 μL DDQ solution (toluene, 10 mM) and diluted with 3 mL CH_2Cl_2/ethanol (3:1). Absorption spectra of the diluted solution were taken and porphyrin yield was assessed photometrically assuming $\varepsilon_{420} = 500{,}000\ M^{-1}cm^{-1}$.

5,15-Bis-(*p*-chlorophenyl)-10-(*p*-tolyl)bilane (24). A sample of **12-diol** (0.09 g, 0.17 mmol; prepared by reduction of **12** as described for **6-diol** and **10-diol**) was dissolved in neat pyrrole (1 mL, 80 equiv) and deaerated for 5 min with argon, then $BF_3{\cdot}O(Et)_2$ (2.5 M stock solution in CH_2Cl_2, 69 μL) was added. After stirring for 10 min at room temperature, the brown solution was diluted with 50 mL CH_2Cl_2 and washed with 0.1 N NaOH. The organic layer was washed with water and dried (Na_2SO_4). The pale yellow solution was concentrated to dryness and the resulting red viscous oil was chromatographed on silica (4 x 20 cm, hexanes/ethyl acetate/triethylamine 80:20:1). A fast-moving green pigment eluted first followed by a yellowish component. The latter was collected and solvent was evaporated without delay, affording a slightly off-white product. Yield 65 mg (62%). mp 85-87 °C; ^1H NMR ($CDCl_3$) δ 7.91 (bs, 4 H, NH), 7.30 - 7.25 (m, 4 H, Ar-H), 7.16 - 7.12 (m, 8 H, Ar-H), 6.72 - 6.68 (m, 4 H, pyrrole-H), 6.17 - 6.14 (m, 4 H, pyrrole-H), 5.92 - 5.89 (m, 3 H, 2 pyrrole-H and 1 *meso*-H), 5.46 - 5.44 (m, 2 H, *meso*-H), 2.33 (s, 3 H, CH_3); LD-MS ($C_{38}H_{32}N_4Cl_2$) calcd mass 614.2, obsd 614.8.

5,15-Bis(*p*-chlorophenyl)-10,20-bis(*p*-tolyl)porphyrin (25). The mixture of **24** (65 mg, 0.11 mmol), *p*-tolualdehyde (12.5 μL, 0.11 mmol), and 10.5 mL CH_2Cl_2 was purged with argon for 5 min. Then TFA (4 μL, 0.5 equiv) was injected and the solution was stirred for 20 min at room temperature. Then DDQ (72 mg, 3 equiv) was added and stirring was continued for 1 h. The solvent was evaporated and the remaining black material was chromatographed on silica (4 x 20 cm, CH_2Cl_2), affording 5 mg (6%). This sample proved to consist of the title compound and two other porphyrin isomers upon analysis by mass spectrometry (see text).

Deuterium exchange experiments (10 → 27 → 10). In a 5 mm NMR tube, 5 mg **10** was dissolved in 0.5 mL CD_2Cl_2 then 10 μL CF_3CO_2D (13 equiv) was added via syringe. The spectral change was followed over 30 h with near-complete exchange of the 3 and 7-pyrrolic protons. Then the light-red solution was diluted with 20 mL CH_2Cl_2, washed with 0.1 N NaOH, water, and dried (Na_2SO_4). The residue after evaporation of the solvent was vacuum-dried and transferred to another NMR tube. 0.5 mL $CDCl_3$ was added followed by 20 μL CF_3CO_2H (26 equiv) and the reaction mixture was incubated for 24 h, again forming a red solution. The ^1H NMR spectrum showed recovery of the 3 and 7-pyrrolic protons. Comparison of the integration of the H_2 (6.93 ppm) and the H_3 (6.20 ppm) signals showed the recovery to be 70% complete.

Deuterium exchange experiments (12 → 26). Following the same procedure as above, 6 mg **12** in 0.5 mL $CDCl_3$ (0.023 M) was exposed to 15 equiv CF_3CO_2D (0.35 M) for 30 h, affording the product with deuterium exchange at the 3 and 7-positions (see spectrum C in Figure 5). ^1H NMR ($CDCl_3$) δ 10.75 (s, TFA-H), 7.78 (AA'BB', *p*-ClArH), 7.48 (AA'BB', *p*-ClArH), 7.17 (collapsed dd, *p*-tolyl-H), 6.96 (s, 2,8-pyrrole-H), 6.23 (m, trace of residual 3,7-pyrrole-H), 5.62 (s, *meso*-H), 2.36 (s, CH_3).

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