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Investigation of Complementary Reactions of a Dipyrromethane with a Dipyrromethanemonocarbinol Leading to a 5-Isocorrole

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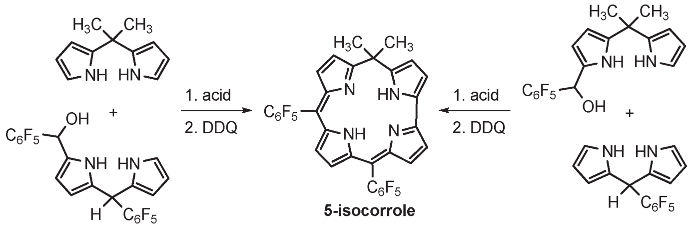

Two complementary dipyrromethane + dipyrromethanemonocarbinol routes to a meso-substituted 5-isocorrole were investigated. While both routes could afford the identical 5-isocorrole, self-condensation of the different dipyrromethanemonocarbinol precursors could potentially lead to a second porphyrinoid of different structure (a porphyrin or a porphodimethene). The two reaction routes were examined to compare the distribution of porphyrinoid products, probe the effect of key reaction parameters on the product distribution, and identify conditions for the efficient preparation of the 5-isocorrole so that its spectral properties and stability toward light and air could be assessed. For each route, a systematic survey of reaction parameters was performed via analytical-scale reactions monitored for the yields of the 5-isocorrole and self-condensation product by HPLC. The two reaction routes were found to afford very different product distributions in accordance with the anticipated nucleophilicity of the dipyrromethane and dipyrromethanemonocarbinol precursors. The most promising reaction condition ($InCl_3$, 0.32 mM) was performed on a preparative-scale providing the 5-isocorrole in an isolated yield of 31% (102 mg). Spectroscopic analysis was consistent with the 5-isocorrole structure. The stability of the 5-isocorrole in dilute solution upon exposure to light and air was assessed by UV−vis spectroscopy and HPLC and was found to be excellent.

Introduction

Porphyrinic macrocycles with core structures altered relative to porphyrin are of interest as their properties and potential applications may complement prototypical porphyrins.[1] One structural alteration of particular interest is the incorporation of an sp^3-hybridized carbon atom at one of the bridging meso positions as exemplified by phlorins and 5-isocorroles (pseudocorrole[2]).[3] The sp^3-hybridized carbon atom disrupts macrocycle conjugation, altering the electronic structure and rendering such porphyrinoids nonaromatic. Additionally, the presence of the sp^3-hybridized carbon atom introduces a structural perturbation due to the tetrahedral geometry at that position.

Our initial interest in porphyrinoids bearing an sp^3-hybridized meso-position was directed toward phlorins. This interest stemmed from the intriguing structural relationship of phlorins to the better known porphyrin and corrole species. Corroles have received recent attention, in part,

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[1] (a) Sessler, J. L.; Weghorn, S. *Expanded, Contracted, and Isomeric Porphyrins*; Elsevier: Oxford, 1997. (b) Jasat, A.; Dolphin, D. *Chem. Rev.* **1997**, *97*, 2267–2340. (c) Sessler, J. L.; Gebauer, A.; Vogel, E. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 2, pp 1−54. (d) Sessler, J. L.; Gebauer, A.; Weghorn, S. J. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 2, pp 55−124. (e) Misra, R.; Chandrashekar, T. K. *Acc. Chem. Res.* **2008**, *41*, 265–279.

[2] The name "isocorrole" was first applied to the entirely different (2.0.1.0)-type isomer of corrole. For that reason, 5-isocorrole has also been called "pseudocorrole" in the literature: Orlewska, C.; Maes, W.; Toppet, S.; Dehaen, W. *Tetrahedron Lett.* **2005**, *46*, 6067–6070.

[3] Sessler, J. L.; Zimmerman, R. S.; Bucher, C.; Kral, V.; Andrioletti, B. *Pure Appl. Chem.* **2001**, *73*, 1041–1057.

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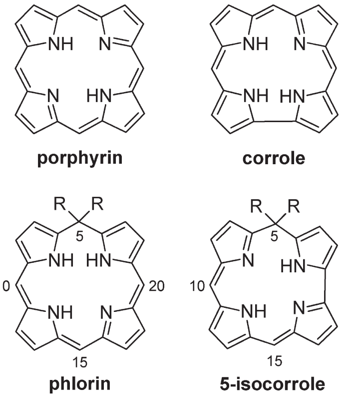
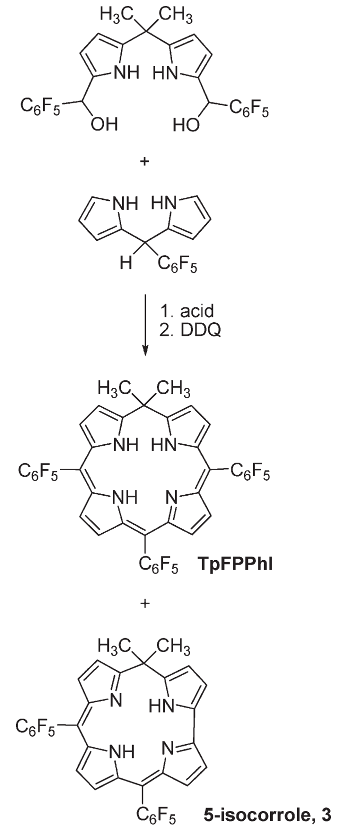
due to their ability to stabilize metal ions in high oxidation states[4] and the observation of catalysis complementary to metalloporphyrins.[5] Presumably, the distinctive coordination chemistry of corroles stems from their greater electron richness and smaller core cavity relative to porphyrins. Like corroles, phlorins bear three "pyrrole-like" N−H groups in their core rendering them trianionic upon deprotonation and metal insertion. Yet, like porphyrins, phlorins lack the core contraction of the direct bipyrrole linkage. Interestingly, unlike either corroles or porphyrins, phlorins bear an sp^3 hybridized carbon atom at one of the meso positions. Taken together, the phlorin structure is complementary to corroles and porphyrins in interesting ways. Unfortunately, many phlorins are unstable toward light and air.[6] Thus, we began our work by investigating the impact of sterically bulky[7] or electron-withdrawing[8] peripheral meso substituents on phlorin stability.



SCHEME 1. Dipyrromethane + Dipyrromethanedicarbinol Route to a Phlorin Bearing Electron-Withdrawing Substituents (TpFPPhl) That Also Provided a 5-Isocorrole Byproduct in Low Yield



While attempting to prepare a phlorin bearing pentafluorophenyl substituents at the three sp^2-hybridized meso positions (TpFPPhl, Scheme 1),[8] a second green pigment was observed in a subset of the reaction conditions. The UV−vis spectrum of the pigment was remarkably similar to that of TpFPPhl, and the ^{1}H NMR spectrum of the pigment showed features consistent with a porphyrinoid, albeit one of lower symmetry than TpFPPhl. Laser desorption mass spectral (LD-MS) analysis found the molecular weight of the pigment to be lower than TpFPPhl by approximately a pentafluorophenyl substituent and a carbon atom. Based on this preliminary spectral characterization, the second pigment appeared to be 5-isocorrole **3** [5,5-dimethyl-10,15-bis(pentafluorophenyl)isocorrole]. This is not unreasonable as the 5-isocorrole could have arisen from acidolytic cleavage of one of the carbinol groups of the dipyrromethanedicarbinol precursor[9] followed by formation of the direct bipyrrole linkage upon oxidation with DDQ.[10]

Although the 5-isocorrole was observed inconsistently and in low quantity, we were intrigued by its structure. Like phlorins, the structure of 5-isocorroles is complementary to porphyrins and corroles, but in a different way. 5-Isocorroles bear two internal N−H groups like porphyrins, while the size of the core cavity is similar to corroles (due to the direct bipyrrole linkage). Unlike either corroles or porphyrins, 5-isocorroles bear an sp^3-hybridized carbon atom. Perhaps the properties (e.g., coordination chemistry) of 5-isocorroles will complement porphyrins, corroles, and phlorins in interesting ways. Relative to these better studied porphyrinoids; little is known about 5-isocorroles. Only a small number of free base 5-isocorroles have been reported.[11] All bear an oxygen atom at the sp^3-hybridized position (a hydroxyl or methoxy group), and all were obtained upon oxidation of a corrole (twice as a byproduct from attempts to demetallate copper or silver corrole complexes[11b,c]). Additionally, three

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(4) (a) Vogel, E.; Will, S.; Schulze-Tilling, A; Neumann, L.; Lex, J.; Bill, E.; Trautwein, A. X.; Wieghardt, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 731–735. (b) Erben, C.; Will, S.; Kadish, K. M. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 2, pp 233−300. (c) Gross, Z. *J. Biol. Inorg. Chem.* **2001**, *6*, 733–738. (d) Ghosh, A.; Steene, E. *J. Inorg. Biochem.* **2002**, *91*, 423–436. (e) Gross, Z.; Gray, H. B. *Comments Inorg. Chem.* **2006**, *27*, 61–72.

(5) (a) Gross, Z.; Gray, H. B. *Adv. Synth. Catal.* **2004**, *346*, 165–170. (b) Aviv, I.; Gross, Z. *Chem. Commun.* **2007**, 1987–1999.

(6) Jeandon, C.; Krattinger, B.; Ruppert, R.; Callot, H. J. *Inorg. Chem.* **2001**, *40*, 3149–3153.

(7) LeSaulnier, T. D.; Graham, B. W.; Geier, G. R., III. *Tetrahedron Lett.* **2005**, *46*, 5633–5637.

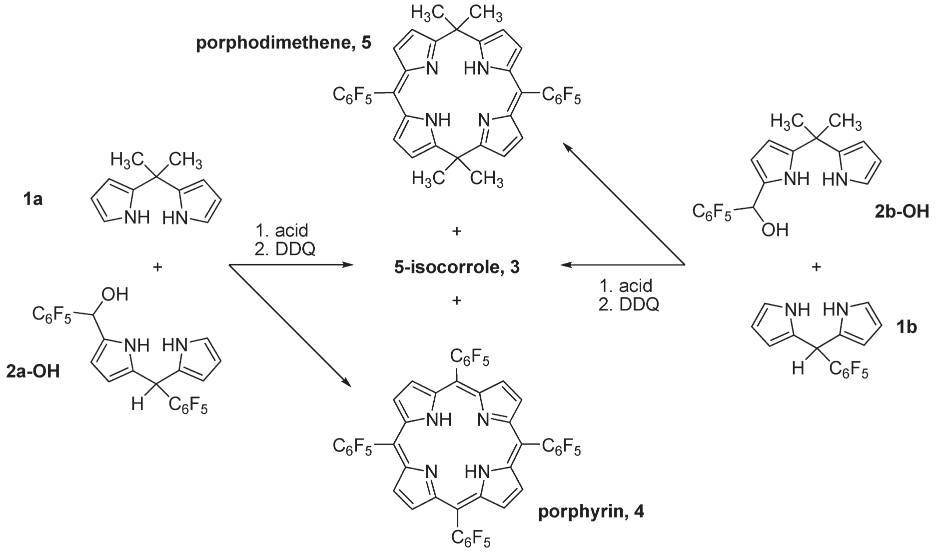
(8) O'Brien, A. Y.; McGann, J. P.; Geier, G. R., III. *J. Org. Chem.* **2007**, *72*, 4084–4092.

(9) Braaten, K. C.; Gordon, D. G.; Aphibal, M. M.; Geier, G. R., III. *Tetrahedron* **2008**, *64*, 9828–9836.

(10) Formation of a direct bipyrrole linkage upon oxidation has been observed in the synthesis of meso-substituted corroles from tetrapyrrane species and in the synthesis of expanded porphyrins: (a) Gryko, D. T. *Eur. J. Org. Chem.* **2002**, 1735–1743. (b) Nardis, S.; Monti, D.; Paolesse, R. *Mini-Rev. Org. Chem.* **2005**, *2*, 355–374. (c) Sessler, J. L.; Seidel, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 5134–5175.

(11) (a) Nardis, S.; Pomarico, G.; Fronczek, F. R.; Vicente, M. G. H.; Paolesse, R. *Tetrahedron Lett.* **2007**, *48*, 8643–8646. (b) Mandoj, F.; Nardis, S.; Pomarico, G.; Paolesse, R. *J. Porphyrins Phthalocyanines* **2008**, *12*, 19–26. (c) Stefanelli, M.; Shen, J.; Zhu, W.; Mastroianni, M.; Mandoj, F.; Nardis, S.; Ou, Z.; Kadish, K. M.; Fronczek, F. R.; Smith, K. M.; Paolesse, R. *Inorg. Chem.* **2009**, *48*, 6879–6887.

SCHEME 2. **Complementary Dipyrromethane + Dipyrromethanemonocarbinol Routes Leading to a 5-Isocorrole and/or a Self-Condensation Product (a Porphyrin or a Porphodimethene)**



nickel complexes of 5-isocorroles have been reported.[2,12] One was obtained in low quantity upon nickel insertion to a biphenylenyl bridged biscorrole.[12] The other two were obtained as low yield (~3%) byproducts of nickel-templated MacDonald [2 + 2] condensation reactions of a dipyrromethane with a bisformyldipyrromethane.[2] Nickel-templated condensation of a dipyrromethane with a monoformyldipyrromethane improved the yield of one of the nickel 5-isocorroles to 10%.[2] To the best of our knowledge, a targeted synthesis of a free-base 5-isocorrole has not been reported. Motivated by the intriguing structure of 5-isocorroles and by the limited prior work in this area, we undertook studies toward the synthesis of 5-isocorrole **3**. The results of this work are reported herein.[13]

5-Isocorrole **3**, with pentafluorophenyl substituents at the two sp^2-hybridized meso positions, was targeted for three key reasons. (1) A small quantity of the 5-isocorrole had already been isolated in the course of our previous studies of reactions leading to TpFPPhl. This authentic sample aided the detection and identification of the compound in this study. (2) The stability toward light and air of free base 5-isocorroles is not established. The incorporation of electron-withdrawing groups would increase the likelihood of obtaining a stable product.[8,14] (3) The electron-withdrawing substituents were expected to influence the reaction pathway leading to the 5-isocorrole. This important issue is discussed in greater detail in following sections.

Complementary two-step, one-flask reactions[15] of a dipyrromethane with a dipyrromethanemonocarbinol were selected for the synthesis of 5-isocorrole **3** (Scheme 2). Both routes were attractive as dipyrromethanemonocarbinols have the free α-pyrrole position required for formation of the direct bipyrrole linkage upon oxidation.[10] Additionally, the use of dipyrromethanecarbinol species in the synthesis of porphyrinoids is well established.[8,14,16−18] However, both routes share a potential drawback. The dipyrromethanemonocarbinol species can undergo self-condensation leading to an alternative porphyrinoid byproduct. In fact, the self-condensation of dipyrromethanemonocarbinols is an important route for the preparation of *trans*-A_2B_2-porphyrins.[16a] Interestingly, the two reaction routes shown in Scheme 2 give rise to different self-condensation products—a porphyrin **4** (meso-tetrakispentafluorophenylporphyrin) from the self-condensation of **2a-OH** and a porphodimethene **5** [bis(pentafluorophenyl)calix[4]phyrin] from the self-condensation of **2b-OH**. The success of either reaction route depends on suppression of dipyrromethanemonocarbinol self-condensation. Thus, we sought to explore the distribution of the 5-isocorrole and self-condensation products for both reaction routes, determine the effect of reaction conditions on the product distribution, and identify conditions for the preparation and purification of the 5-isocorrole. Additionally, we sought to examine the spectral properties of the 5-isocorrole and assess its stability in dilute solution toward light and air.

To explore the complementary reaction routes, required precursors were prepared and a systematic investigation of

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(12) Jerome, F.; Barbe, J.-M.; Gros, C. O.; Guilard, R.; Fischer, J.; Weiss, R. *New J. Chem.* **2001**, *25*, 93–101.

(13) A portion of this work was presented at the 238th ACS National Meeting: Geier, G. R., III; Long, A. C.; Fowler, R. L.; Flint, D. L.; O'Brien, A. Y. *Abstr. Papers Am. Chem. Soc.* **2009**, *238*, 719.

(14) Geier, G. R., III; Chick, J. F. B.; Callinan, J. B.; Reid, C. G.; Auguscinski, W. P. *J. Org. Chem.* **2004**, *69*, 4159–4169.

(15) Two-step, one-flask syntheses of porphyrinoids involve oligomer formation during an acid catalyzed condensation step, followed by an oxidation step whereby reduced precursors are converted to the porphyrinoids. The oxidation step is carried out without isolation of the products from the condensation step. Lindsey, J. S. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; pp 45−118.

(16) (a) Rao, P. D.; Littler, B. J.; Geier, G. R., III; Lindsey, J. S. *Org. Chem.* **2000**, *65*, 1084–1092. (b) Rao, P. D.; Dhanalekshmi, S.; Littler, B. J.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7323–7344. (c) Geier, G. R., III; Callinan, J. B.; Rao, D. P.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2001**, *5*, 810–823.

(17) (a) Cho, W. S.; Kim, H. J.; Littler, B. J.; Miller, M. A.; Lee, C. H.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 7890–7901. (b) Balasubramanian, T.; Strachan, J. P.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7919–7929. (c) Guilard, R.; Gryko, D. T.; Canard, G.; Barbe, J.-M.; Koszarna, B.; Brandes, S.; Tasior, M. *Org. Lett.* **2002**, *4*, 4491–4494. (d) Gryko, D. T.; Tasior, M.; Koszarna, B. *J. Porphyrins Phthalocyanines* **2003**, *7*, 239–248.

(18) Geier, G. R., III; Grindrod, S. C. *J. Org. Chem.* **2004**, *69*, 6404–6412.

the effect of key reaction parameters (acid catalyst, acid catalyst concentration, quantity of DDQ oxidant, condensation time, and ratio of dipyrromethane to dipyrromethanemonocarbinol) was carried out for each route. The yields of the 5-isocorrole and self-condensation product in the analytical-scale reactions were assessed by HPLC. Preparative-scale reactions were performed under the best conditions identified from the analytical-scale studies, and the 5-isocorrole was isolated and characterized. The stability of the 5-isocorrole in dilute solution toward light and air was examined by monitoring changes in UV−vis spectra and HPLC chromatograms.

Results and Discussion

Preparation of Building Block Molecules. Dipyrromethanes **1a**,**b**[19] and monoacyl dipyrromethane **2a**[20] (precursor to **2a-OH**) were prepared according to the literature. Monoacyl dipyrromethane **2b** (precursor to **2b-OH**) was prepared in a yield of 41% (0.76 g) from dipyrromethane **1a** in accordance with literature conditions for the preparation of related monoacyl dipyrromethanes.[16a] Dipyrromethane-monocarbinol species **2a-OH** and **2b-OH** were prepared immediately prior to use by $NaBH_4$ reduction of **2a** or **2b** and were used without purification as reported in the literature.[16a] We found that the reduction of **2b** required the addition of 75 equiv of $NaBH_4$ rather than the more typical 25 equiv for the reduction to come to completion in the usual reaction time of ~30 min.

Preparation of Analytical Quantities of 5-Isocorrole 3 and Porphodimethene 5. To develop methodology for monitoring analytical-scale reactions leading to 5-isocorrole **3** and the self-condensation product **4** or **5**, a small amount of each compound was required. Porphyrin **4** is commercially available. A very small amount of the 5-isocorrole had been previously isolated in our earlier work on the preparation of TpFPPhl. Additional 5-isocorrole was prepared from a reaction of **1a** + **2a-OH** (0.500 mmol each, 2.5 mM each) in CH_2Cl_2 at room temperature for 5 h catalyzed by $Dy(OTf)_3$ (3.2 mM) followed by oxidation with DDQ (3 equiv relative to **1a** or **2a-OH**). These reaction conditions had previously provided detectable levels of the 5-isocorrole in our earlier studies of a different reaction route leading to TpFPPhl. While these conditions were not expected to be optimal, they did afford the 5-isocorrole in a yield of 6% (18 mg) after purification by filtration through a silica pad and crystallization from CH_2Cl_2/pentane. The porphodimethene **5** is a known compound,[21] although it had not been previously prepared by the self-condensation of **2b-OH**. As we had the precursor monoacyl dipyrromethane **2b** on hand, we elected to attempt the preparation of the porphodimethene by self-condensation of **2b-OH**. Reaction of **2b-OH** (0.40 mmol, 5.0 mM) in CH_2Cl_2 at room temperature for 30 min catalyzed by $InCl_3$ (3.2 mM) followed by oxidation with DDQ (1 equiv relative to **2a-OH**) afforded the porphodimethene in a yield of 21% (29 mg). The reaction conditions were derived from methodology previously used to prepare trans-A_2B_2-porphyrins from the self-condensation of dipyrromethane-monocarbinols.[16c] NMR, mass spectrometric, and UV−vis analyses of the porphodimethene were in agreement with reported values for the compound prepared by alternative dipyrromethane + aldehyde/ketone routes leading to the porphodimethene in yields of 6−7%.[21]

HPLC Method for Assessing the Production of the 5-Isocorrole and Self-Condensation Products in Analytical-Scale Reactions. To perform a large number of analytical-scale reactions in parallel, methodology for the efficient monitoring of the yield of the three porphyrinoids was required. An HPLC method used in our recent investigation of reaction routes leading to TpFPPhl was adapted to this study.[8] The method entails oxidation of an aliquot of the condensation reaction mixture with DDQ, basification by the addition of triethylamine, filtration of the oxidized reaction mixture through a silica pad to remove insoluble and strongly polar species, and analysis by HPLC. The separation and quantitation of the 5-isocorrole and porphyrin obtained from the reaction of **1a** + **2a-OH** was achieved without event. However, under identical chromatographic conditions, the 5-isocorrole and the porphodimethene obtained from the reaction of **1b** + **2b-OH** were found to coelute. Fortunately, we found that the two compounds could be spectrally resolved so that it was not necessary to modify the chromatographic conditions. The use of different chromatography conditions to assess the product distribution from the two reaction routes would have been problematic as normal phase columns equilibrate slowly. An expanded discussion of the spectral resolution of the 5-isocorrole and the porphodimethene as well as a summary of control experiments, reproducibility experiments, detector response calibration, calculation of porphyrinoid yield, and representative chromatograms may be found in the Supporting Information.

Survey of Acid Catalysis Conditions. To examine the effect of acid catalyst and acid catalyst concentration on the yields of 5-isocorrole **3** and self-condensation product **4** or **5**, a survey of acid catalysis conditions was carried out for both reaction routes. Five acid catalysts [TFA, $InCl_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, and $Dy(OTf)_3$] at five concentrations (0.32, 1.0, 3.2, 10, and 32 mM, and in some cases 0.010 and 0.032 mM)[22] were investigated. Each reaction was monitored for the yield of the 5-isocorrole and self-condensation product at 0.25, 1, and 4 h. TFA is a benchmark acid for two-step, one-flask reactions leading to porphyrinoids,[15] and the four mild Lewis acids have been found to be well-suited for dipyrromethanecarbinol routes to porphyrin[16c] and other porphyrinoids.[8,14,18]

Results from representative conditions affording good yields of the 5-isocorrole or self-condensation product are summarized in Table 1. Illustrative plots of the yield of the 5-isocorrole or self-condensation product as a function of $InCl_3$ concentration are provided in Figure 1 (see the Supporting Information for the complete set of plots).

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[19] (a) Littler, B. J.; Miller, M. A.; Hung, C.-H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1391–1396. (b) Laha, J. K.; Dhanalekshmi, S.; Taniguchi, M.; Ambroise, A.; Lindsey, J. S. *Org. Process Res. Dev.* **2003**, *7*, 799–812.

[20] Strachan, J. P.; O'Shea, D. F.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 3160–3172.

[21] (a) Bernatkova, M.; Andrioletti, B.; Kral, V.; Rose, E.; Vaissermann, J. *J. Org. Chem.* **2004**, *69*, 8140–8143. (b) Dolensky, B.; Kroulik, J.; Sessler, J. L.; Dvorakova, H.; Bour, P.; Bernatkova, M.; Bucher, C.; Lynch, V. *J. Am. Chem. Soc.* **2004**, *126*, 13714–13722.

[22] The quantity of acid is reported in concentration units of molarity for convenience of comparison of reaction conditions. However, $InCl_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, and $Dy(OTf)_3$ are poorly soluble in some of the solvents, and the reaction mixtures were heterogeneous as reported previously.[16c]

TABLE 1. Comparison of Macrocycle Yields from the Reaction of 1a + 2a-OH and 1b + 2b-OH from Representative Conditions Examined in the Survey of Acid Catalysis Conditions[a]

			1a + 2a-OH		**1b + 2b-OH**	
entry	acid	[acid], mM	% yield of 5-isocorrole[b]	% yield of porphyrin[b]	% yield of 5-isocorrole[b]	% yield of porphodimethene[b]
1	TFA	0.32	5.2	2.1	6.8	31
2	$InCl_3$	0.32	37	2.4	2.1	50
3	$InCl_3$	1.0	31	2.7	1.7	49
4	$Sc(OTf)_3$	0.32	27	6.1	6.1	51
5	$Yb(OTf)_3$	0.32	26	4.7	4.7	50
6	$Yb(OTf)_3$	10	27	5.9	7.5	53
7	$Dy(OTf)_3$	1.0	21	6.1	5.3	49

[a] The reactions were performed in CH_2Cl_2 with the indicated reactants (2.5 mM each) on a 5−10 mL scale at room temperature. The reactions were monitored at 0.25, 1, and 4 h. [b] The highest yield (HPLC) at any of the three time points is reported.

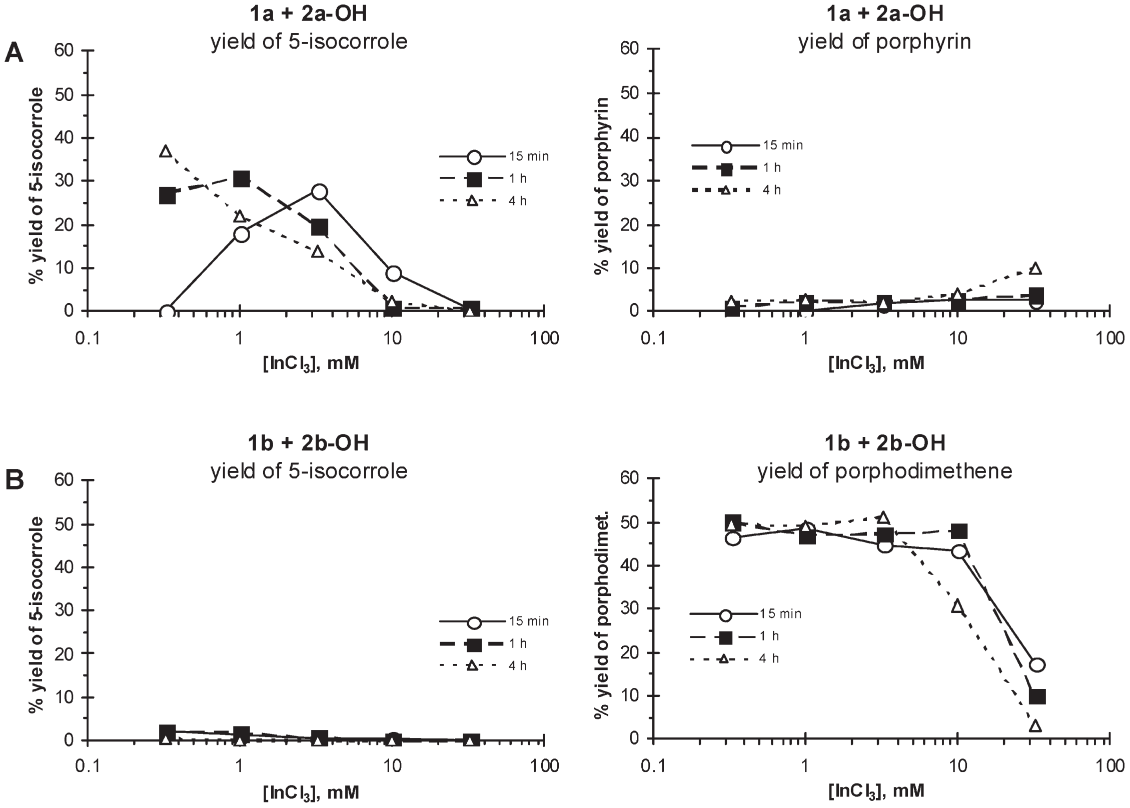

FIGURE 1. Yield of the 5-isocorrole (left panels) and self-condensation product (porphyrin or porphodimethene, right panels) as a function of $InCl_3$ concentration for the reaction of (A) **1a** + **2a-OH** and (B) **1b** + **2b-OH**. The reactions were performed with the indicated reactants (2.5 mM each) in CH_2Cl_2 at room temperature. The reactions were monitored by HPLC.

The most striking result is the observation of very different ratios of the 5-isocorrole to self-condensation product from the complementary reaction routes. In the reaction of **1a** + **2a-OH**, generally more 5-isocorrole than porphyrin was obtained, whereas the reaction of **1b** + **2b-OH** generally led to more porphodimethene than 5-isocorrole. It is clear that the choice of reaction route had a substantial impact on product distribution, with the reaction of **1a** + **2a-OH** being the superior route for the preparation of the 5-isocorrole. For this route, a number of conditions provided yields of the 5-isocorrole of 20−40% while limiting porphyrin formation to yields of 2−6%. Catalysis with $InCl_3$ was particularly promising in terms of the yield of the 5-isocorrole and suppression of porphyrin byproduct (Table 1, entries 2 and 3). The suppression of porphyrin formation is important as the chromatographic properties of the two compounds are very similar. Thus, purification of the 5-isocorrole from preparative-scale reactions is more straightforward if less porphyrin is present.

In addition to these key findings, a number of additional observations were made. (1) The precise ratio of products was found to vary somewhat as a function of acid catalyst. For example, in the reaction of **1a** + **2a-OH**, catalysis with $InCl_3$ afforded good yields of the 5-isocorrole and very little porphyrin (Table 1, entries 2 and 3), whereas catalysis with $Sc(OTf)_3$, $Yb(OTf)_3$, and $Dy(OTf)_3$ afforded slightly lower yields of the 5-isocorrole but about twice the level of porphyrin as was observed from catalysis with $InCl_3$ (entries 4−7). In the reaction **1b** + **2b-OH**, similar yields of the porphodimethene were observed from most catalysts, but the level of the 5-isocorrole was found to vary. (2) For each reaction route and acid catalyst, the maximum yield of

TABLE 2. Summary of Results from Reaction Time Course Experiments[a]

entry	reactants	acid	[acid], mM	time, h[b]	% yield of 5-isocorrole[c]	% yield of self-condensation product[d]
1	**1a** + **2a-OH**	$InCl_3$	0.32	2	35	1.4
2	**1a** + **2a-OH**	$InCl_3$	1.0	0.5	32	1.9
3	**1a** + **2a-OH**	Sc(OTf)$_3$	0.32	0.5	28	4.7
4	**1a** + **2a-OH**	Yb(OTf)$_3$	10	1	26	4.5
5	**1a** + **2a-OH**	Dy(OTf)$_3$	1.0	8	25	5.1
6	**1b** + **2b-OH**	TFA	0.32	0.25	7.8	30
7	**1b** + **2b-OH**	$InCl_3$	0.32	0.25	2.7	47
8	**1b** + **2b-OH**	Sc(OTf)$_3$	0.32	0.5	6.8	45
9	**1b** + **2b-OH**	Yb(OTf)$_3$	0.32	4	6.5	47
10	**1b** + **2b-OH**	Dy(OTf)$_3$	1.0	8	7.4	48

[a] The reactions were performed in CH_2Cl_2 with the indicated reactants (2.5 mM each) on a 20 mL scale at room temperature. The reactions were monitored from 1 min to 24 h. [b] The reaction time that first provided the highest yield of the 5-isocorrole. [c] The highest yield of the 5-isocorrole (HPLC) is reported. [d] The yield of the porphyrin (**1a** + **2a-OH**) or porphodimethene (**1b** + **2b-OH**) (HPLC) at the time that the highest yield of the 5-isocorrole was first obtained is reported. The yields reported here are generally within $\sim$2% of the highest yield obtained at any time.

the 5-isocorrole and self-condensation product was generally similar across a wide range of acid concentration. For example, the reaction of **1a** + **2a-OH** mediated by $InCl_3$ afforded a similar yield of the 5-isocorrole across a 10-fold range of acid concentration (Figure 1A). The reaction of **1b** + **2b-OH** mediated by $InCl_3$ afforded a similar level of porphodimethene across a 30-fold range of acid concentration (Figure 1B). The maximum yield of the porphyrinoids may be observed more quickly at higher acid concentration (Figure 1A), nevertheless, a near maximum yield could be obtained across a wide range of acid concentration as long as the condensation reaction time was adjusted. (3) Extremes of acid catalyst concentration were found to impact the product distribution. This was most evident in the reaction of **1a** + **2a-OH** under TFA catalysis. At low TFA concentration, the 5-isocorrole was the major product (albeit in low yield). At high TFA concentration, the porphyrin was the major product (see the Supporting Information). So while the choice of reaction route appears to be the primary determinant of the distribution of products, the precise choice of acid catalyst and catalyst concentration also has an influence.

Investigation of Oxidation Conditions. In previous work,[8,14,18] we found that some two-step, one-flask syntheses of porphyrinoids require exacting conditions for the oxidation step, and occasionally the best oxidation conditions deviate from the stoichiometric quantity of oxidant. Thus, we investigated oxidation conditions for both reaction pathways. We first explored oxidation conditions prior to performing the survey of acid catalyst conditions. Reactions of **1a** + **2a-OH** or **1b** + **2b-OH** [Dy(OTf)$_3$, 3.2 mM] were performed, and aliquots (1.2 mL) of the reaction mixture were transferred to quantities of DDQ (0.5, 1.0, 2.0, 4.0, 8.0, 16, or 32 mg). The stoichiometric quantity of DDQ relative to 5-isocorrole for a 1.2 mL aliquot of crude reaction mixture is 2.04 mg (3 equiv per **1a** or **2a-OH**).[23] The oxidized reaction mixtures were assessed by HPLC and TLC. To further refine the oxidation conditions, the experiment was repeated over a narrower range of DDQ quantities (0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 mg). Once the reaction of **1a** + **2a-OH** ($InCl_3$, 0.32 mM) was found to provide the highest yield of the 5-isocorrole and the lowest level of the porphyrin byproduct, a reaction of **1a** + **2a-OH** ($InCl_3$, 0.32 mM) was performed and aliquots (1.2 mL) were transferred to quantities of DDQ (0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 mg).

For the reaction of **1a** + **2a-OH** under either acid catalyst, the highest yield of the 5-isocorrole was obtained in the range of 1.5−2.5 mg of DDQ. At both higher and lower quantities of DDQ the yield of the 5-isocorrole decreased, and no 5-isocorrole was detected at DDQ quantities of ≥ 8 mg. The yield of porphyrin self-condensation product was less sensitive to the quantity of DDQ with similar yields obtained from 1.5 to 32 mg DDQ. For the reaction of **1b** + **2b-OH**, the highest yield of the 5-isocorrole and the porphodimethene were both in the range of 1.0−4.0 mg DDQ indicating that this reaction route is a little less sensitive to the amount of DDQ than the complementary route. For both reaction routes, the stoichiometric amount of DDQ was found to be appropriate. This amount was used for analytical and preparative-scale reactions.

Reaction Time Course Experiments. Representative reaction conditions identified from the survey of catalysis conditions were performed for the reaction of **1a** + **2a-OH** and **1b** + **2b-OH** with monitoring by HPLC and TLC at time points ranging from 1 min to 24 h. A summary of the reaction conditions investigated and the highest yield of the 5-isocorrole and self-condensation product (porphyrin or porphodimethene) are provided in Table 2. Representative plots of the yield of the 5-isocorrole and self-condensation product as a function of condensation time are provided in Figure 2 (see the Supporting Information for the complete set of plots).

As with the survey of catalysis conditions, the two reaction routes provided very different product distributions. The reaction of **1a** + **2a-OH** afforded the 5-isocorrole as the major product, and the reaction of **1b** + **2b-OH** primarily led to the porphodimethene self-condensation product. The reaction of **1a** + **2a-OH** ($InCl_3$, 0.32 mM) again provided the best result in terms of the yield of the 5-isocorrole and suppression of porphyrin byproduct (Table 2, entry 1). The reaction trajectory provided by all conditions explored showed a turnover and decline in the yield of the 5-isocorrole at extended reaction times (Figure 2A). Such a turnover in yield in two-step, one-flask reactions leading to porphyrinoids is not uncommon,[24] but reactions showing such a

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(23) The stoichiometric amount of DDQ for the porphyrin (self-condensation of **1a-OH**) from a 1.2 mL aliquot of the reaction mixture is 1.02 mg (1.5 equiv relative to **1a-OH**). The stoichiometric amount of DDQ for the porphodimethene (self-condensation of **1b-OH**) from a 1.2 mL aliquot of the reaction mixture is 0.68 mg (1.0 equiv relative to **1b-OH**).

(24) Geier, G. R., III; Lindsey, J. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 677–686.

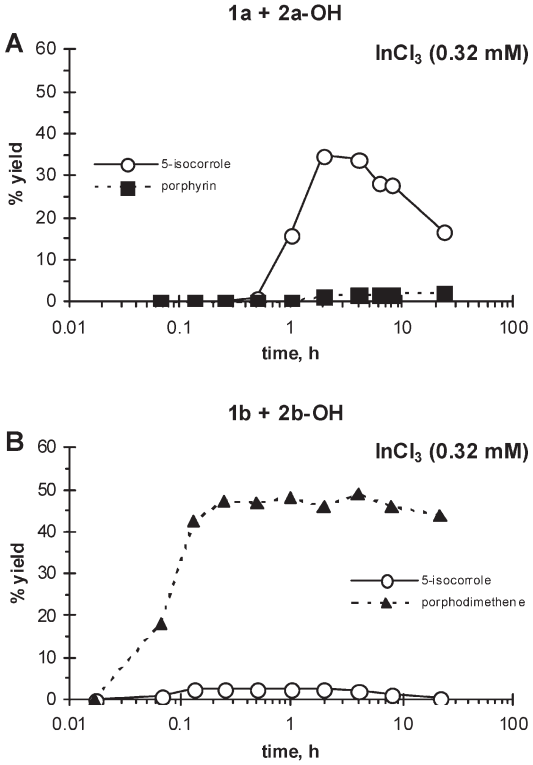

FIGURE 2. Yields of the 5-isocorrole and self-condensation product (porphyrin or porphodimethene) as a function of condensation time. The reactions were performed with the indicated reactants (2.5 mM each) in CH_2Cl_2 at room temperature under catalysis by $InCl_3$ (0.32 mM). The reactions were monitored by HPLC. Note the logarithmic scale for time.

turnover should be monitored so that the DDQ oxidant is added at an appropriate time. Fortunately, the yield trajectory provided by the best reaction condition ($InCl_3$, 0.32 mM) afforded a similarly good yield of the 5-isocorrole over a condensation time of 2−4 h. Thus, the reaction time is not overly exacting for this reaction condition. This contrasts with the majority of the other conditions surveyed (Table 2, entries 2−4) which displayed a turnover in the 5-isocorrole yield at an earlier point in the reaction leading to a shorter window of time for optimal addition of the oxidant.

Other key observations are as follows. (1) The appearance of the low level of porphyrin byproduct closely tracked the production of the 5-isocorrole in reactions of **1a** + **2a-OH**. However, no turnover in porphyrin yield was observed. (2) The appearance of the 5-isocorrole and porphodimethene byproduct also closely tracked each other in reactions of **1b** + **2b-OH** (Figure 2B). Again, at longer reaction times the yield of the 5-isocorrole tended to turnover and decline, while the yield of the porphodimethene remained steady. Similar trajectories were observed across all conditions examined. (3) The yield of the 5-isocorrole and self-condensation products observed in these experiments were similar to those obtained at equivalent time points in the survey of acid catalysis conditions.

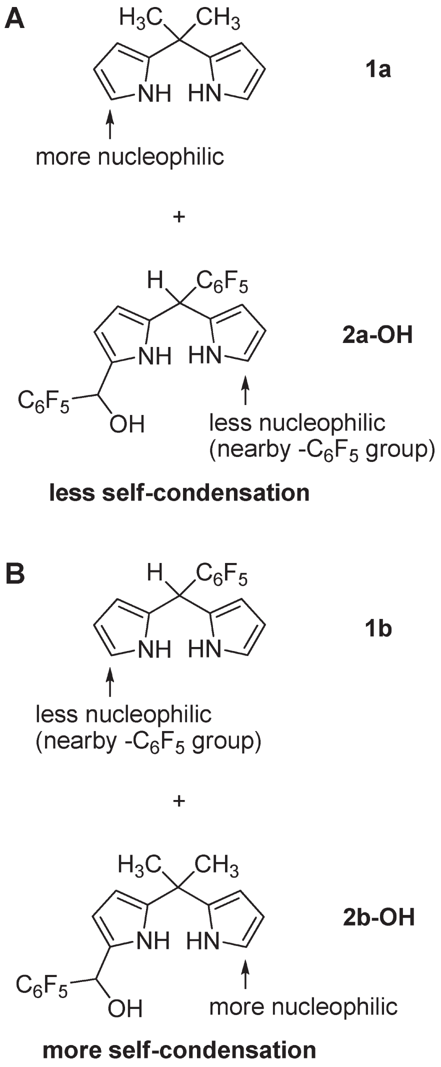

FIGURE 3. Correlation of the level of self-condensation of (A) **2a-OH** or (B) **2b-OH** with differences in the nucleophilicity of the available α-pyrrole positions of the two dipyrromethanes and two dipyrromethanemonocarbinols.

On the Two Reaction Routes. The survey of catalysis conditions and time-course experiments both revealed contrasting product distributions from the complementary reaction routes. The reaction of **1a** + **2a-OH** generally led to the 5-isocorrole, whereas the reaction of **1b** + **2b-OH** predominantly led to self-condensation of **2b-OH**. This finding correlates with anticipated differences in the nucleophilicity of the available α-pyrrole positions of the two dipyrromethanes and two dipyrromethanemonocarbinols (Figure 3). In both reaction routes, there is a competition between the free α-pyrrole positions for reaction with the electrophilic carbinol group of **2-OH**. If the α-pyrrole positions of the dipyrromethane are more nucleophilic than the α-pyrrole position of the dipyrromethanemonocarbinol, then the 5-isocorrole product may be the major porphyrinoid product. If the free α-pyrrole position of the dipyrromethanemonocarbinol is instead more nucleophilic, then the product of self-condensation may predominate. In the reaction of **1a** + **2a-OH**, the pyrrole rings of **1a** are appended to a bridging carbon atom bearing two electron-releasing methyl groups, whereas the pyrrole rings of **2a-OH** are appended to a bridging carbon atom bearing an electron-withdrawing substituent. In the reaction of **1b** + **2b-OH**, the substituents are reversed and **2b-OH** bears pyrrole rings adjacent to a bridging carbon atom with the two methyl substituents. The effect of the substituents at the bridging carbon atom on the various α-pyrrole positions is apparent in the ^{1}H NMR spectra of the dipyrromethanes and dipyrromethanemonocarbinols. In $CDCl_3$, the α-pyrrole protons of **1a** and **2b-OH** are both found at ~6.58 ppm, whereas the analogous protons of **1b** and **2a-OH** are both more deshielded, appearing at ~6.71 ppm.

The apparently profound effect of the substituents at the bridging carbon atom of the dipyrromethanes and dipyrromethanemonocarbinols is important to consider in synthetic planning. It appears that the reaction of a dipyrromethane with a dipyrromethanemonocarbinol will afford the best ratio of the 5-isocorrole to self-condensation product when substituents are present that cause the nucleophilicity of the precursors to differ. For example, replacement of the electron-withdrawing pentafluorophenyl substituent with a phenyl group at the bridging carbon atom of **1b** and **2a-OH** should result in lower selectivity for both reaction routes. We are currently investigating this possibility as well as exploring whether other reaction parameters can be adjusted so as to obtain a satisfactory product ratio.

Investigation of the Ratio of the Dipyrromethane to the Dipyrromethanemonocarbinol. The ratio of dipyrromethane to dipyrromethanemonocarbinol could be an important parameter in suppressing self-condensation as presumably an excess of dipyrromethane would lower the level of self-condensation. With this in mind, we sought to determine if the very low level of porphyrin byproduct obtained from reaction of **1a** + **2a-OH** ($InCl_3$, 0.32 mM) could be further lowered by altering the ratio of the starting materials. Complete suppression of porphyrin formation would simplify purification of the 5-isocorrole as the chromatographic properties of the 5-isocorrole and the porphyrin are very similar. Of course, any improvement in product distribution would need to be weighed against the use of excess dipyrromethane, a synthetic precursor.

We began by exploring nine reaction conditions ranging from equimolar to 10-fold excess of **1a** relative to **2a-OH** (2.5 mM) under conditions of $InCl_3$ catalysis (0.32 mM) in $CHCl_2$ at room temperature. The reactions were monitored at 1, 2, and 4 h. The yield of both the porphyrin and the 5-isocorrole were found to decline with increasing excess of dipyrromethane. At a roughly 5-fold excess of **1a**, neither product was detected. It is possible that the excess dipyrromethane interfered with either the acid catalyst or oxidant necessitating further refinement of reaction conditions. We found it less likely that the oxidation conditions posed a problem as excess **1a** should not consume oxidant (the presence of two methyl groups at the bridging carbon atom renders the dipyrromethane inert toward oxidation). Nevertheless, we explored both possibilities. A survey of $InCl_3$ concentration (0.32, 1.0, 3.2, 10, and 32 mM) was carried out using a fixed ratio of **1a** to **2a-OH** (5:1). The reactions were monitored at 0.25, 1, and 4 h. While porphyrin was not detected under any condition, the yield of the 5-isocorrole was quite low ranging from 2 to 6%. $InCl_3$ (3.2 mM) provided the modestly best result. A survey of DDQ quantity (0.5, 1.0, 2.0, 3.0, 4.0, 8.0, 16, 32 mg) was carried out using aliquots (1.2 mL) from a reaction of **1a** to **2a-OH** (5:1) mediated by $InCl_3$ (3.2 mM). The yield of the 5-isocorrole did increase slightly with increasing DDQ reaching a maximum level of ~7% with 8.0 mg of DDQ. No porphyrin was detected under any condition. Overall, this preliminary survey of reactant ratio found the yield of both products to be suppressed. Whether the same result will be obtained with other substituent combinations remains to be determined. Fortunately, the inability to further suppress porphyrin formation without lowering the yield of the 5-isocorrole was not a major problem in this study as we were able to purify the 5-isocorrole from the low level of porphyrin byproduct by crystallization (vide infra).

Preparative-Scale Synthesis of 5-Isocorrole 3. Preparative-scale reactions were performed to confirm findings from analytical-scale experiments, to determine whether the 5-isocorrole could be conveniently purified from the low level of porphyrin byproduct, and to obtain sufficient quantity of the 5-isocorrole for characterization and stability studies. Preparative-scale reactions were carried out under the best conditions identified from the analytical-scale experiments: reaction of **1a** + **2a-OH** (0.500 mmol, 2.5 mM each), $InCl_3$ (0.32 mM), in CH_2Cl_2 at room temperature. Reactions were monitored by HPLC, and DDQ (3 equiv relative to **1a** or **2a-OH**) and triethylamine (5 equiv relative to $InCl_3$) were added when the yield of the 5-isocorrole reached a maximum (generally at a reaction time of 2 h). The crude, oxidized reaction mixture was assessed by HPLC. The yields of the 5-isocorrole and porphyrin determined from an aliquot prior to oxidation were 34% and 1.4%, respectively, in good agreement with results from earlier analytical-scale reactions (Table 2, entry 1). After oxidation of the entire reaction mixture, the HPLC yields of the 5-isocorrole, and porphyrin were found to be 37% and 1.8%, respectively. The crude reaction mixture was passed through a silica pad to remove polar impurities. Silica gel chromatography with CH_2Cl_2/hexanes (1:5) afforded the 5-isocorrole (132 mg) still contaminated with a very low level of porphyrin but largely devoid of other impurities. The percentage by mass of the 5-isocorrole was found by HPLC and ^{1}H NMR analyses to be 97% and 98%, respectively. The good agreement between HPLC and NMR analyses is supportive of accurate HPLC detector response calibration. The approximate yield of the 5-isocorrole after chromatography (corrected for the low level of porphyrin) is in agreement with the yield estimated by HPLC during reaction monitoring and after oxidation. Isolation of the 5-isocorrole from the porphyrin was achieved by crystallization from CH_2Cl_2/hexanes (31%, 102 mg). Absence of the porphyrin was confirmed by HPLC and ^{1}H NMR analyses (Supporting Information). The isolated yield and scale compare favorably to syntheses of other porphyrinoids via dipyrromethanecarbinol routes.[8,14,16−18]

Characterization of 5-Isocorrole 3. The UV−vis spectrum of the 5-isocorrole is quite similar to that of TpFPPhl, consistent with an interruption of macrocycle conjugation due to an sp^3-hybridized meso-carbon atom. LD-MS and high-resolution FAB-MS data were satisfactory. ^{13}C NMR analysis ($CDCl_3$) revealed 18 peaks in the region of 105−185 ppm consistent with the 18 sp^2-hybridized carbon atoms of the 5-isocorrole ring (Supporting Information). Peaks at 25 and 39 ppm were also observed from the equivalent methyl substituents and the sp^3-hybridized meso-carbon atom, respectively. In addition, weak, split signals from carbon atoms of the pentafluorophenyl substituents were observed. ^{1}H NMR analysis ($CDCl_3$) revealed two separate signals at 13.7 and 13.9 ppm for the two core N−H groups (Supporting Information). The assignment of the N−H protons was supported by the absence of correlation to carbon atoms in the HMQC spectrum. The downfield location of the N−H signals is consistent with the absence of overall macrocycle aromaticity. The observation of two distinct signals for the N−H protons is in accord with reported NMR data for 5-isocorroles bearing hydroxy[11b,c] or methoxy[11a] substituents at the sp^3-hybridized carbon atom. The presence of two distinct peaks for the N−H protons is suggestive of slow tautomerism. The tautomeric form of the 5-isocorrole drawn in Scheme 1 was supported by COSY and NOESY analysis (Supporting Information), and it is the same tautomer recently reported for a 5-isocorrole bearing a hydroxy group at the sp^3-hybridized position based on X-ray crystallography.[11c] The β-pyrrole region of the NMR spectrum revealed four sets of doublets (7.15, 7.04, 7.02, and 6.82 ppm) consistent with protons on pyrrole rings lacking a N−H proton, two sets of doublets of doublets (6.97 and 6.49 ppm) consistent with protons on a pyrrole ring bearing a N−H proton, and overlapping signals at 6.36 ppm. In addition, a singlet was observed at 1.8 ppm with integration in accord with two equivalent methyl groups. A further discussion of the assignment of the ^{1}H NMR spectrum may be found in the Supporting Information.

Stability of 5-Isocorrole 3. The stability toward light and air of the 5-isocorrole in dilute solution was investigated. Similar to our previous studies of the stability of meso-substituted corroles,[14] octaphyrins,[18] and phlorins,[7,8] solutions of the 5-isocorrole were prepared in solvents of varying polarity (hexanes, toluene, CH_2Cl_2, THF, ethyl acetate, acetone, acetonitrile, and methanol), and changes in UV−vis spectra were followed as a function of time of exposure to standard room lighting (i.e., light from conventional overhead fluorescent lighting). The solutions were monitored for a period of two weeks. A representative plot of overlaid UV−vis spectra (CH_2Cl_2) is shown in Figure 4A (see the Supporting Information for the complete set of overlaid spectra). A representative plot of the 5-isocorrole absorbance (717 nm, CH_2Cl_2) as a function of time is shown in Figure 4B (see the Supporting Information for the complete set of plots).

As shown by the illustrative data, dilute solutions of the 5-isocorrole are very stable over 14 days of exposure to light and air. The solution in CH_2Cl_2 retained better than 99% of its initial absorbance at 717 nm. The other solutions generally displayed similar stability. To confirm the results of UV−vis monitoring, fresh solutions were prepared in CH_2Cl_2 or methanol, exposed to light, and the disappearance of the 5-isocorrole was monitored by HPLC for a period of 14 days. Consistent with the UV−vis monitoring, little change was observed in the peak area of the 5-isocorrole for both solutions. The 5-isocorrole appears to be quite stable toward light and air, even more so than the closely related phlorin, TpFPPhl.[8] It will be interesting to determine if such stability is a general feature of 5-isocorroles or whether the electron-withdrawing pentafluorophenyl substituents substantially enhance the stability as is the case with TpFPPhl.

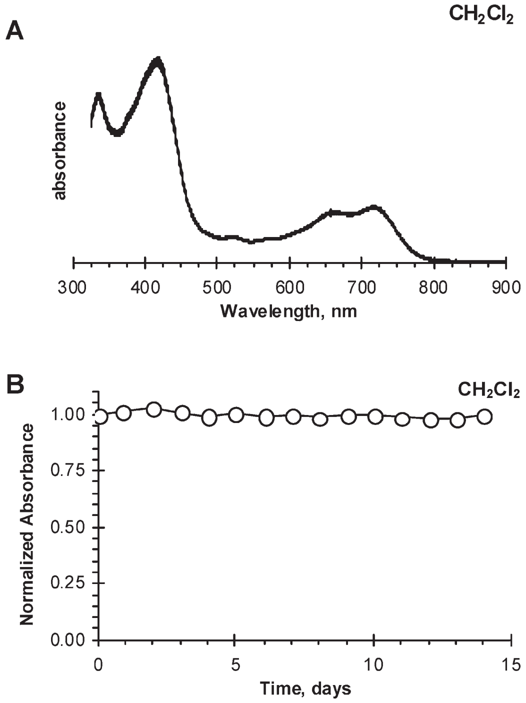

FIGURE 4. (A) Overlaid UV−vis spectra of a solution of the 5-isocorrole in CH_2Cl_2 recorded after exposure to light and air over a period of 14 days. (B) Plot of absorbance as a function of time of exposure to light for a solution of the 5-isocorrole in CH_2Cl_2 (717 nm).

Conclusions

Complementary reactions of a dipyrromethane with a dipyrromethanemonocarbinol were investigated to examine the distribution of a 5-isocorrole and self-condensation product (a porphyrin or a porphodimethene), probe the effect of key reaction parameters on the product distribution, and identify appropriate reaction conditions for the preparation of the 5-isocorrole so that its spectral properties and stability could be assessed. The two reaction routes produced very different results across a wide range of conditions with the reaction of **1a** + **2a-OH** primarily providing the 5-isocorrole and the reaction of **1b** + **2b-OH** primarily affording the self-condensation product (a porphodimethene). Reaction conditions (acid catalyst, acid concentration, reaction time, and ratio of dipyrromethane to dipyrromethanemonocarbinol) had some effect on the product distribution; however, the primary determinant was the choice of reaction route. The substantially different outcomes obtained from the complementary routes show that the choice of starting materials can have a profound impact on the outcome of the reaction. The product distributions observed from the two reaction routes are consistent with anticipated differences in the nucleophilicity of the dipyrromethanes and dipyrromethanemonocarbinol species. The best yield of the 5-isocorrole with the lowest level of porphyrin byproduct was obtained from the reaction of **1a** + **2a-OH** ($InCl_3$, 0.32 mM). Preparative-scale reactions were in accord with the results of analytical-scale reactions monitored by HPLC. On the preparative-scale, the low level of porphyrin byproduct could be removed by crystallization with minimal impact on the isolated yield of the 5-isocorrole. Spectral characterization was consistent with the proposed 5-isocorrole structure. Dilute solutions of the 5-isocorrole were found to be quite stable toward light and air. The fairly efficient preparation of the 5-isocorrole along with the observation of interesting spectral properties and good stability provides encouragement for further studies of this compound and for investigations of 5-isocorroles bearing a broader array of substituents.

Experimental Section

1-Pentafluorobenzoyl-5,5-dimethyldipyrromethane (2b). Following a general monoacylation procedure from the literature,[16a] ethylmagnesium bromide (12.5 mL, 12.5 mmol, 1 M in THF) was added dropwise over 15 min to a solution of 5,5-dimethyldipyrromethane **1a** (0.871 g, 5.00 mmol) in dry THF (5 mL) under argon. The reaction mixture was stirred for 10 min at room temperature and then cooled to −78 °C. A suspension of *S*-2-pyridyl pentafluorobenzothioate[16a] (1.53 g, 5.00 mmol) in THF (10 mL) was added over 1 min. The solution was kept at −78 °C for 10 min, the cooling bath was removed, and the reaction was allowed to stir for an additional 40 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (50 mL). The mixture was poured into CH_2Cl_2 (50 mL), washed with water (50 mL), and dried over Na_2SO_4, and the solvent was removed providing a brown viscous liquid. Flash column chromatography [silica, CH_2Cl_2/hexanes (2:1) to CH_2Cl_2/hexanes (4:1)] afforded a pale yellow viscous liquid. Crystallization (EtOH/H_2O) provided light tan crystals (760 mg, 41%): mp 111−113 °C; ^{1}H NMR ($CDCl_3$) δ 9.34 (s, 1H), 1.70 (s, 6H), 6.13 (m, 1H), 6.16 (m, 1H), 6.19 (m, 1H), 6.62 (m, 1H), 6.71 (m, 1H), 8.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.7, 35.9, 105.0, 108.3, 108.6, 114.0 (t, J = 21 Hz), 118.0, 122.5, 130.5, 136.2, 137.6 (d, J = 243 Hz), 142.1 (d, J = 257 Hz), 143.9 (d, J = 251 Hz), 151.1, 171.5; EI-MS obsd 368, calcd 368; IR ν_{max} (thin film)/cm^{-1} 1617. Anal. Calcd for $C_{18}F_5OH_{13}N_2$: C, 58.70; H, 3.56; N, 7.61. Found: C, 58.74; H, 3.51; N, 7.57.

Bis(pentafluorophenyl)calix[4]phyrin (Porphodimethene, 5). Following a literature procedure,[16a] the reduction of **2b** (147 mg, 0.400 mmol) with $NaBH_4$ (1.14 g, 30.0 mmol) in THF/methanol (32 mL, 3:1) afforded the corresponding monocarbinol **2b-OH** which was used without purification. The monocarbinol was dried under vacuum for 30 min and then immediately subjected to self-condensation in the presence of $InCl_3$ (56.6 mg, 0.256 mmol) in CH_2Cl_2 (80 mL) for 30 min at room temperature. Oxidation of the reaction mixture was carried out by the addition of DDQ (90.8 mg, 0.400 mmol) at room temperature. The reaction mixture was basified by the addition of triethylamine (0.178 mL, 1.28 mmol) and allowed to stir for 30 min. The reaction mixture was filtered through a pad of silica gel and eluted with CH_2Cl_2 until the eluant was no longer red/orange. The filtrate was concentrated to a bright orange solid. Flash column chromatography [silica, CH_2Cl_2/hexanes (1:5)] afforded a red powder (54 mg) upon evaporation of the solvent. Crystallization (CH_2Cl_2/hexanes) provided red needle crystals upon slow evaporation of the CH_2Cl_2 solvent (29 mg, 21%). Analytical data were in agreement with those previously reported[21] (see the Supporting Information for the ^{1}H and ^{13}C NMR spectra).

HPLC Determination of the Yield of the 5-Isocorrole (3), Porphyrin (4), and Porphodimethene (5). Analytical-scale reactions of **1a** + **2a-OH** and **1b** + **2b-OH** were monitored for the yield of the 5-isocorrole and porphyrin or porphodimethene by adaptation of a literature method for the analysis of TpFPPhl in crude reaction mixtures.[8] An aliquot (1.2 mL) of a condensation reaction mixture was transferred by adjustable pipet to a 1.8 mL microcentrifuge tube containing DDQ (2.00 mg, 0.00881 mmol), and the mixture was vortex mixed for 2−5 s. Triethylamine (1 equiv relative to acid) was added. A portion of the oxidized reaction mixture (1.0 mL) was transferred via adjustable pipet to a Pasteur pipet filled two-thirds full with silica gel (~1.5 g). The sample was eluted with three 1-mL portions of CH_2Cl_2, and solvent was driven off the column with a hand-held pipet tool. The eluant was transferred to an autosampler vial and capped. HPLC analysis was performed with an injection volume of 1 μL, a normal-phase silica column (Alltech, Altima, 4.6 mm × 250 mm), using an isocratic solvent mixture of 92% hexanes and 8% acetone. The hexanes solvent was water saturated by storing over water prior to use. The solvent flow rate was controlled as follows: T = 0−8 min, 1 mL/min; T = 8−9 min, linear increase to 2 mL/min; T = 9−14 min, 2 mL/min; T = 14−15 min, linear decrease to 1 mL/min. The 5-isocorrole, porphyrin, and porphodimethene eluted at 6.9, 8.2, and 6.9 min, respectively. Detection was performed at 335 nm (5-isocorrole), 417 nm (porphyrin), and 423 nm (5-isocorrole and porphodimethene). The yields of the 5-isocorrole and porphyrin or porphodimethene were determined from the peak area by calibration of the detector response to each compound. The peak area for the porphodimethene required correction to account for the contribution of the coeluting 5-isocorrole. Representative chromatograms and further details on the analysis method development, control and reproducibility experiments, HPLC calibration, and spectral resolution of the 5-isocorrole and porphodimethene may be found in the Supporting Information.

Survey of Acid Catalysis Conditions. Following a literature procedure,[16a] immediately prior to the condensation reactions, the monoacyl dipyrromethane [**2a** (192 mg, 0.375 mmol) or **2b** (138 mg, 0.375 mmol)] was reduced to the corresponding dipyrromethanemonocarbinol (**2a-OH** or **2b-OH**) with $NaBH_4$ [**2a** (0.355 g, 9.38 mmol); **2b** (1.07 g, 28.1 mmol) in THF/methanol (30 mL, 3:1)]. The reduction reactions were monitored by TLC [**2a**, alumina, CH_2Cl_2; **2b** alumina, EtOAc/CH_2Cl_2 (1:5)]. After drying under vacuum for 30 min, the monocarbinol was dissolved in CH_2Cl_2, dipyrromethane **1a** (65.3 mg, 0.375 mmol) or **1b** (117 mg, 0.375 mmol) was added to the flask, and the volume was brought to 150 mL by adding CH_2Cl_2. Reactions were performed at room temperature in tightly capped 20-mL vials that were stirred with a micro stir bar. Solid acids were weighed into all reaction vials prior to the beginning of the reaction sequence for the day, and each reaction was initiated by the addition of 5−10 mL of the reactant solution via volumetric pipet. Reactions involving TFA were initiated by the addition of TFA to reaction vials already containing 5 mL of the reactant solution. The reactions were monitored by HPLC at 0.25, 1, and 4 h as described above. TLC was performed on the crude, oxidized mixture [silica, CH_2Cl_2/hexanes (1:1)].

Reaction Time-Course Experiments. Reaction monitoring as a function of time was performed as described above for the survey of acid catalysis conditions with the exception of using a 20 mL reaction volume. The reactions were monitored by HPLC as described above at 1 min, 4 min, 8 min, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, and 24 h. Selected conditions were also monitored at 6 h. TLC was performed on the crude, oxidized mixture [silica, CH_2Cl_2/hexanes (1:1)].

5,5-Dimethyl-10,15-bis(pentafluorophenyl)isocorrole (3). The reduction of **2a** (253 mg, 0.500 mmol) with $NaBH_4$ (473 mg, 12.5 mmol) in THF/methanol (40 mL, 3:1) afforded the corresponding monocarbinol **2a-OH** which was used without purification.[16a] The monocarbinol was dried under vacuum for 30 min and then immediately subjected to condensation with **1a** (87.1 mg, 0.500 mmol) in the presence of $InCl_3$ (14.2 mg, 0.0640 mmol) in CH_2Cl_2 (200 mL) at room temperature. At 1.5 h, the reaction was monitored by HPLC as described above, and the yield of the 5-isocorrole was found to be satisfactory. At a total reaction time of 2 h, the reaction mixture was oxidized by the addition of DDQ (330 mg, 1.50 mmol) at room temperature. After 5 min, triethylamine (0.045 mL, 0.32 mmol) was added, and the mixture was stirred at room temperature for a further 1 h. An aliquot (1.2 mL) of the oxidized reaction mixture was removed for HPLC analysis. The remaining reaction mixture was filtered through a pad of silica gel and eluted with CH_2Cl_2 until the eluant was no longer green. The filtrate was concentrated and adsorbed onto silica gel (10 g), concentrated to dryness, and purified by chromatography [silica, CH_2Cl_2/hexanes (1:5)] affording the 5-isocorrole contaminated with a low level of porphyrin (132 mg, 98% 5-isocorrole by mass). Crystallization by slow evaporation of CH_2Cl_2 from a CH_2Cl_2/hexanes solution provided purple crystals of the 5-isocorrole (102 mg, 31%) devoid of porphyrin: IR λ_{abs} (toluene, $\varepsilon \times 10^3$) 339 (30.7), 423 (39.4), 671 (9.74), 731 (11.4); ^1H NMR ($CDCl_3$) δ 1.81 (s, 6H), 6.38 (m, 2H), 6.49 (dd, J = 2.5, 3.7 Hz, 1H), 6.83 (d, J = 4.7 Hz, 1H), 6.98 (dd, J = 2.6, 3.7 Hz, 1H), 7.01 (d, J = 4.6 Hz, 1H). 7.03 (d, J = 4.7 Hz, 1H), 7.16 (d, J = 4.6 Hz, 1H), 13.70 (s, 1H), 13.87 (s. 1H) ; ^{13}C NMR ($CDCl_3$) δ 24.9, 38.6, 108.3, 110.9, 111.7, 112.0, 114.0, 118.5, 119.9, 122.4, 124.2, 125.8, 126.3, 133.8, 134.4, 135.2, 141.0, 147.9, 149.1, 153.7, 161.2, 183.4 (additional weak signals were present in the region of 135−147 ppm due to carbon atoms bearing a fluorine); LD-MS obsd 658.1 (M^+), calcd 658.1; HRMS (FAB) 659.1288 ($M + H^+$), calcd 659.1288 ($C_{33}H_{17}F_{10}N_4$).

5-Isocorrole Stability Experiments (UV−vis)[8]. In a darkened laboratory, solutions of 5-isocorrole **3** were prepared in hexanes, toluene, CH_2Cl_2, THF, ethyl acetate, acetone, acetonitrile, and methanol. The concentration of each solution was adjusted so that the maximum absorbance in the visible range (705−730 nm) was between 0.3 and 0.5. UV−vis spectra were recorded in the dark, and then the solutions were exposed to room lights (conventional overhead fluorescent lighting). Spectra were recorded at 15 min, 30 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 8 h, 1 d, 1.5 d, 2 d, 3 d, 4 d, 5 d, 6 d, 7 d, 8 d, 9 d, 10 d, 11 d, 12 d, 13 d, and 14 d of continuous exposure to room lights. Decomposition of the 5-isocorrole was inferred from changes in the intensity of the visible band (705−730 nm). Data were normalized with respect to the maximum absorbance in the visible range prior to exposure to light. As a control, an analogous experiment was performed with solutions of the 5-isocorrole (hexanes, CH_2Cl_2, and MeOH) maintained in the dark.

5-Isocorrole Stability Experiments (HPLC)[8]. In a darkened laboratory, solutions of 5-isocorrole **3** were prepared in CH_2Cl_2 and MeOH. The concentration of each solution was adjusted so that the initial peak area was between 600 and 700 area units. The samples were analyzed in the dark by HPLC using the same analysis parameters as described above for analysis of oxidized reaction mixtures, and then the solutions were exposed to light (conventional overhead fluorescent lighting). Chromatograms were recorded at 15 min, 1 h, 2 h, 4 h, 6, h 8 h, 1 d, 1.5 d, 2 d, 3 d, 4 d, 5 d, 6 d, 7 d, 8 d, 9 d, 12 d, 13 d, and 14 d of continuous exposure to room lights. Decomposition of the 5-isocorrole was inferred by a decline in the peak area.

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Supporting Information Available: General experimental methods; discussion of HPLC method development, control and reproducibility experiments, and calibration; discussion of spectral resolution of the 5-isocorrole and porphodimethene, discussion of the calculation of porphyrinoid yield from HPLC peak area; representative chromatograms of reaction mixtures; plots of the yield of the 5-isocorrole and self-condensation product as a function of acid concentration; plots of the yield of the 5-isocorrole and self-condensation product as a function of condensation reaction time; data on the stability of the 5-isocorrole; NMR spectra of **2b** and porphodimethene **5**; data on the purity of the 5-isocorrole; discussion of the assignment of the ^1H NMR spectrum of the 5-isocorrole; and NMR spectra of the 5-isocorrole. This material is available free of charge via the Internet at http://pubs.acs.org.