JOC Article

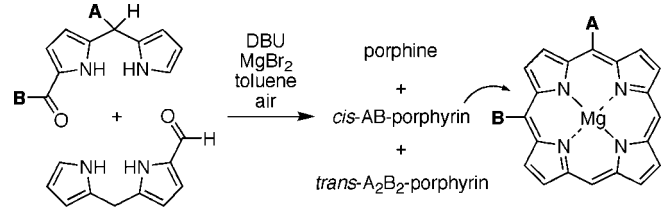
Rational or Statistical Routes from 1-Acyldipyrromethanes to *meso*-Substituted Porphyrins. Distinct Patterns, Multiple Pyridyl Substituents, and Amphipathic Architectures

Dilek Kiper Dogutan, Marcin Ptaszek, and Jonathan S. Lindsey*

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

jlindsey@ncsu.edu

Received March 14, 2008



New methodology is described for the synthesis of porphyrins bearing four (A_4, *cis*-A_2B_2, *cis*-ABC_2, *trans*-A_2B_2) or fewer (A, *cis*-AB, *cis*-A_2, *trans*-A_2) *meso* substituents. The method entails condensation of two 1-acyldipyrromethanes in the presence of a metal salt ($MgBr_2$, 3 mol equiv) and a noncoordinating base (DBU, 10 mol equiv) in a noncoordinating solvent (toluene) with heating (conventional or microwave irradiation) and exposure to air. The rational synthesis of *trans*-A_2B_2- or *trans*-A_2-porphyrins was achieved via condensation of two identical 1-acyldipyrromethanes. The statistical synthesis of various *meso*-substituted porphyrins was achieved via condensation of two nonidentical 1-acyldipyrromethanes. Both routes possess attractive features including (1) no scrambling, (2) good yield (up to 60%) at high concentration (100 mM) for the macrocycle-forming step, (3) reasonable scope (aryl, heteroaryl, alkyl, or no substituent), (4) short reaction time (~2 h) via microwave irradiation, (5) magnesium porphyrins as the products, which easily undergo demetalation, and (6) facile chromatographic purification. A key advantage of the statistical route is to obtain a *cis*-substituted porphyrin without the corresponding *trans* isomer. For example, reaction of an A/B-substituted 1-acyldipyrromethane and the fully unsubstituted 1-formyldipyrromethane gave the magnesium chelates of three porphyrins: the *trans*-A_2B_2-porphyrin, the "hybrid" *cis*-AB-porphyrin, and porphine (no *trans*-AB-porphyrin can form), which were readily demetalated and separated as the free base species. Altogether 26 1-acyldipyrromethanes and 26 target porphyrins have been prepared, including many with two different pyridyl substituents. One set of amphipathic porphyrins includes *cis*-A_2B_2- or *cis*-A_2BC-porphyrins wherein A = pentyl and B/C = pyridyl (*o*-, *m*-, *p*-). Taken together, the rational and statistical routes enable facile conversion of readily available 1-acyldipyrromethanes to diverse porphyrins bearing 1−4 *meso* substituents for which access is limited via other methods.

Introduction

Porphyrins bearing distinct patterns of *meso* substituents are of interest for a broad range of applications. A number of rational synthetic routes to *meso*-substituted porphyrins have been developed that rely on dipyrromethane building blocks (Scheme 1). The routes provide access to ABCD-porphyrins (route I),[1,2] *trans*-A_2B_2-porphyrins (route II),[3–5] *trans*-AB-porphyrins (route III),[6,7] and even porphine (route IV),[8] which

(1) Rao, P. D.; Dhanalekshmi, S.; Littler, B. J.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7323–7344.
(2) Zaidi, S. H. H.; Fico, R. M., Jr.; Lindsey, J. S. *Org. Process Res. Dev.* **2006**, *10*, 118–134.
(3) Littler, B. J.; Ciringh, Y.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 2864–2872.
(4) Rao, P. D.; Littler, B. J.; Geier, G. R., III; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 1084–1092.
(5) Sharada, D. S.; Muresan, A. Z.; Muthukumaran, K.; Lindsey, J. S. *J. Org. Chem.* **2005**, *70*, 3500–3510.
(6) Fan, D.; Taniguchi, M.; Yao, Z.; Dhanalekshmi, S.; Lindsey, J. S. *Tetrahedron* **2005**, *61*, 10291–10302.
(7) Taniguchi, M.; Balakumar, A.; Fan, D.; McDowell, B. E.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2005**, *9*, 554–574.

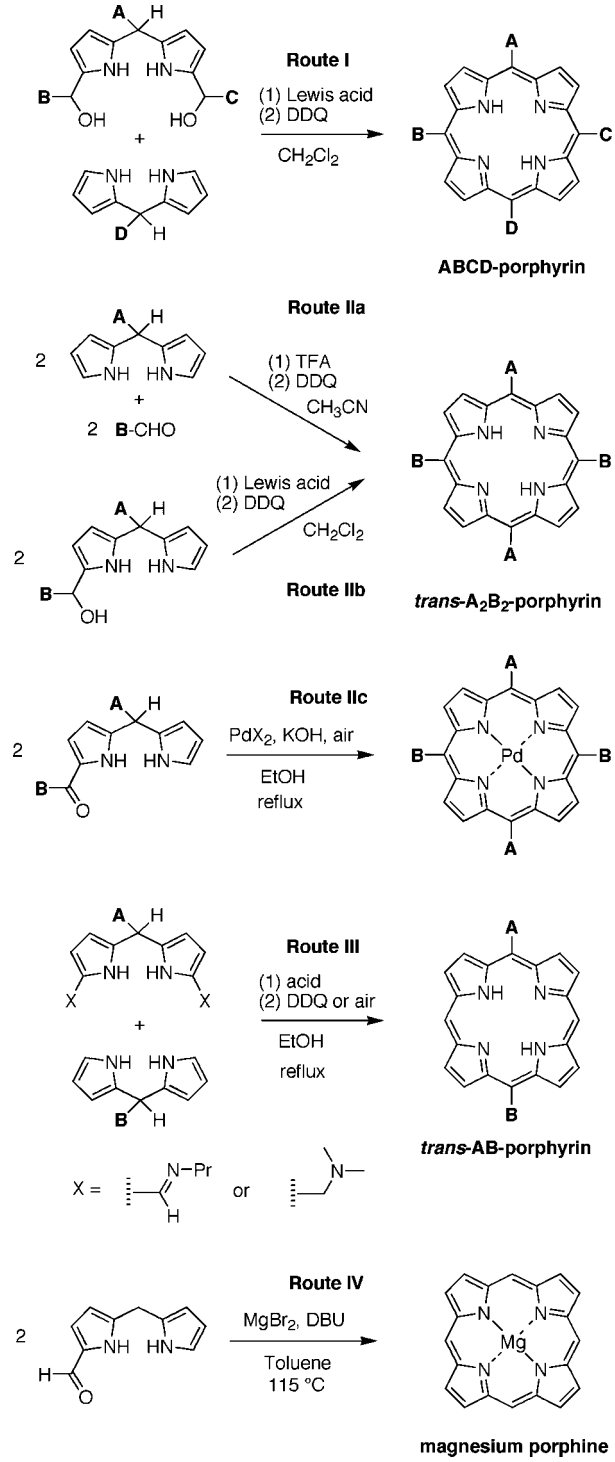
10.1021/jo800588n CCC: $40.75 © 2008 American Chemical Society
Published on Web 07/19/2008

lacks *meso* substituents altogether. Porphyrins bearing fewer than four *meso* substituents also can be prepared by route II (*trans*-A_2-porphyrins) and route III (A-porphyrins). Such sparsely substituted porphyrins can be further derivatized at the open *meso* positions by halogenation followed by palladium-mediated coupling reactions[9] or by nucleophilic addition followed by oxidation.[10]

Inspection of routes I−IV might suggest unlimited access to porphyrins bearing any type and pattern of *meso* substituents. Setting aside the generic limitation of modest yield that afflicts almost all routes in porphyrin chemistry, at least two significant and specific limitations remain in routes I−III: (1) Certain types of substituent patterns, particularly for sparsely substituted porphyrins (e.g., *cis*-A_2, *cis*-AB, and A), remain difficult to access.[11] Route I, which provides versatile access to porphyrins bearing four distinct substituents (i.e., ABCD-porphyrins), in principle should provide access to porphyrins with fewer numbers of substituents. However, the ABCD synthesis fails in such cases owing to the poor reactivity of primary carbinols in the dipyrromethane-dicarbinol (B, C substituents = H) upon acid-catalyzed condensation with the dipyrromethane.[12] (2) Certain types of substituents are incorporated with difficulty in most of the routes shown in Scheme 1, including heterocyclic groups and alkyl groups. In both cases, the conditions for acid-catalyzed condensation (routes I, IIa, IIb, III) are either incompatible with the substituents (heterocyclic groups) or provide poor reactivity (alkyl groups), despite extensive studies of acid catalysis conditions.[2,12–15] The chief problem with many nitrogen heterocycles (e.g., pyridyl) lies in the complexation of the heterocycle with the acid catalyst, resulting in neutralization of the acid and often precipitation of the complex. Some improvement has been achieved by use of modified acid catalysts but the conditions lack generality.[16–19] The chief problem with alkyl groups stems from scrambling (i.e., fragmentation and undesired recombination) to give a mixture of porphyrins.[1,12,20]

Heterocyclic and alkyl groups are of interest for biomedical applications and for studies in supramolecular chemistry. In this regard, porphyrins bearing pyridyl groups[21] have been used for DNA intercalation,[22–26] DNA cleavage,[26,27] DNA labeling,[28] telomerase[29] or acetylcholinesterase[30] inhibition, prion binding,[31] superoxide dismutase mimicry,[32] photodynamic inactivation,[33,34]

SCHEME 1



(8) Dogutan, D. K.; Ptaszek, M.; Lindsey, J. S. *J. Org. Chem.* **2007**, *72*, 5008–5011.
(9) Sharman, W. M.; van Lier, J. E. *J. Porphyrins Phthalocyanines* **2000**, *4*, 441–453.
(10) Senge, M. O. *Acc. Chem. Res.* **2005**, *38*, 733–743.
(11) Wiehe, A.; Shaker, Y. M.; Brandt, J. C.; Mebs, S.; Senge, M. O. *Tetrahedron* **2005**, *61*, 5535–5564.
(12) Geier, G. R., III; Callinan, J. B.; Rao, P. D.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2001**, *5*, 810–823.
(13) Geier, G. R., III; Littler, B. J.; Lindsey, J. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 701–711.
(14) Geier, G. R., III; Littler, B. J.; Lindsey, J. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 712–718.
(15) Speckbacher, M.; Yu, L.; Lindsey, J. S. *Inorg. Chem.* **2003**, *42*, 4322–4337.
(16) Gryko, D.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 2249–2252.
(17) Gryko, D. T.; Tasior, M. *Tetrahedron Lett.* **2003**, *44*, 3317–3321.
(18) Goncalves, D. P. N.; Ladame, S.; Balasubramanian, S.; Sanders, J. K. M. *Org. Biomol. Chem.* **2006**, *4*, 3337–3342.
(19) Goncalves, D. P. N.; Sanders, J. K. M. *Synlett* **2007**, 591–594.
(20) Geier, G. R., III; Lindsey, J. S. *Tetrahedron* **2004**, *60*, 11435–11444.
(21) Sliwa, W.; Zujewska, T.; Mielniczak, M. *Chem. Heterocycl Compd.* **1993**, 617–628.
(22) Bejune, S. A.; Shelton, A. H.; McMillin, D. R. *Inorg. Chem.* **2003**, *42*, 8465–8475.
(23) Wu, S.; Li, Z.; Ren, L. G.; Chen, B.; Liang, F.; Zhou, X.; Jia, T.; Cao, X. P. *Bioorg. Med. Chem.* **2006**, *14*, 2956–2965.
(24) Shelton, A. H.; Rodger, A.; McMillin, D. R. *Biochemistry* **2007**, *46*, 9143–9154.
(25) Wang, K.; Zhang, Z.; Wu, L.; Li, Z. Y. *Chem. Biodiversity* **2007**, *4*, 514–522.
(26) (a) Bigey, P.; Frau, S.; Loup, C.; Claparols, C.; Bernadou, J.; Meunier, B. *Bull. Soc. Chim. Fr.* **1996**, *133*, 679–689. (b) Yellappa, S.; Seetharamappa, J.; Rodgers, L. M.; Chitta, R.; Singhal, R. P.; D'Souza, F. *Bioconjugate Chem.* **2006**, *17*, 1418–1425.
(27) Ishikawa, Y.; Yamakawa, N.; Uno, T. *Bioorg. Med. Chem.* **2007**, *15*, 5230–5238.
(28) Balaz, M.; Holmes, A. E.; Benedetti, M.; Proni, G.; Berova, N. *Bioorg. Med. Chem.* **2005**, *13*, 2413–2421.

radiosensitization,[35] binding to nanoparticles,[36] and assembly into micelles,[37] bilayer lipid membranes,[38] molecular squares,[39] arrays,[40] oligomers,[41,42] and light-harvesting architectures.[43] Several examples have been reported of porphyrins that bear both pyridyl and alkyl groups.[23,24,44–52] Most of the porphyrins bearing fewer than four identical pyridyl groups have been formed by statistical reactions, which give multiple products.

The limitations posed by sparsely substituted porphyrin architectures and heterocyclic or alkyl groups often are intertwined: the target porphyrin often contains one or two heterocyclic or alkyl groups as required to achieve the desired polarity and functionality, while sparse substitution is desired to maintain a compact size and low molecular weight. To broaden access to sparsely substituted porphyrins and porphyrins bearing heterocyclic or alkyl groups requires consideration of new routes to porphyrins. Several years ago we found serendipitously that two 1-acyldipyrromethane molecules would condense under basic metal-mediated conditions to give the corresponding *trans*-A_2B_2-porphyrin (route IIc, Scheme 1).[5] The conditions employed a palladium reagent and KOH in refluxing ethanol and afforded the palladium porphyrin. The 1-acyldipyrromethane condensation provided a more concise route to the *trans*-A_2B_2-porphyrin than that of route IIb, which employs the condensation of dipyrromethane-1-carbinol molecules. We were attracted to basic conditions because we felt such conditions would circumvent the twin problems of acidolysis leading to scrambling that occurs with alkyl and other types of groups and acid-neutralization/complexation that occurs with heterocyclic substituents. However, the formation of the palladium porphyrin represented a limitation in scope given that removal of palladium requires treatment of the porphyrin with strong acid.

To exploit the approach illustrated in route IIc and overcome the fundamental limitations, we embarked on a program to identify conditions that (i) are nonacidic, (ii) use a readily removable and inexpensive metal, and (iii) provide broad scope. We ultimately found that a noncoordinating solvent and base (e.g., toluene and DBU) with a magnesium halide ($MgBr_2$) support the condensation to give the corresponding magnesium(II) porphyrins. We have already reported the use of these conditions in the synthesis of magnesium porphine (route IV)[8] and in a quite different route wherein a 1-acylbilane undergoes intramolecular cyclization to give the magnesium porphyrin.[53] The use of $MgBr_2$ in toluene containing DBU for porphyrin formation has some commonality with conditions used for the insertion of magnesium into free base porphyrins.[54]

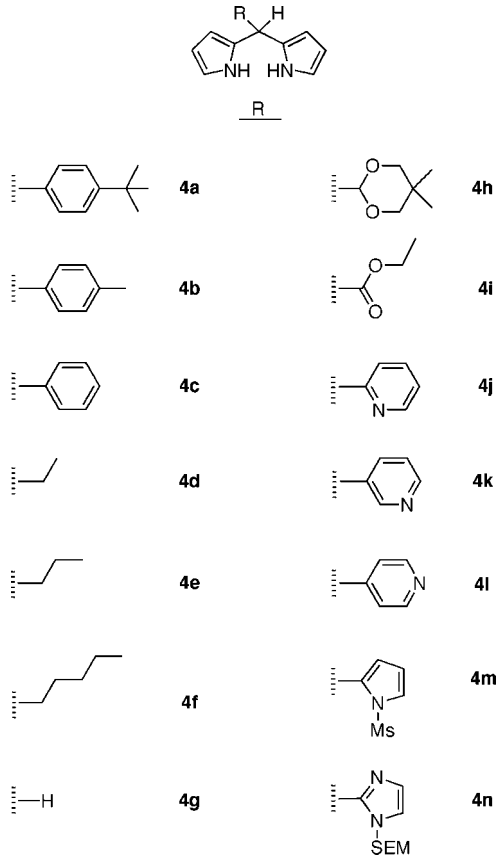
In this paper we report the development of the basic, magnesium-mediated conditions for condensation of 1-acyldipyrromethanes and the application of these conditions to give diverse *meso*-substituted porphyrins. The paper is organized as follows. Part 1 describes the synthesis of 26 1-acyldipyrromethanes with emphasis on a broad survey of functional groups as well as a focus on alkyl and pyridyl substituents. Part 2 summarizes the key conditions for the 1-acyldipyrromethane condensation; extensive studies are contained in Supporting Information. Part 3 reports the application of the conditions to the synthesis of *trans*-A_2B_2-porphyrins or *trans*-A_2-porphyrins (numbered **1**). Part 4 describes the use of statistical reactions wherein two nonidentical 1-acyldipyrromethanes undergo condensation, which has been used to gain access to sparsely substituted porphyrins of the type *cis*-A_2, *cis*-AB, and A (numbered **2**) and *cis*-ABC_2-porphyrins containing two pentyl groups and two nonidentical pyridyl groups (numbered **3**). Altogether 26 target porphyrins have been prepared via these routes. Taken together, the approaches described herein support the synthesis of diverse porphyrins bearing substituents (alkyl, aryl, heterocyclic) in a variety of patterns.

Results and Discussion

1. Synthesis of 1-Acyldipyrromethanes. 1-Acyldipyrromethanes are typically prepared by formation of a dipyrromethane followed by acylation. In this study, we examined a set of 1-acyldipyrromethanes possessing diverse groups (electron-rich, electron-deficient, heteroaryl, alkyl, bulky, H) at the *meso* (5-) or 1-positions. Multigram quantities of dipyrromethanes are available by condensation of an aldehyde with excess pyrrole in the presence of acid.[55] The 14 dipyrromethanes examined herein are shown in Chart 1. Dipyrromethanes **4a**,[53] **4b**,[2] **4c**,[55] **4d**,[56] **4e**,[48] **4f**,[55] **4g**,[55] **4h**,[57] **4i**,[58] **4j**,[16] **4k**,[16] **4l**,[16] and **4n**[59] are known; however, a more recent procedure (using $InCl_3$)[55] was

(29) (a) Han, H. Y.; Hurley, L. H. *Trends Pharmacol. Sci.* **2000**, *21*, 136–142. (b) Shi, D. F.; Wheelhouse, R. T.; Sun, D. Y.; Hurley, L. H. *J. Med. Chem.* **2001**, *44*, 4509–4523.
(30) Namgoong, S. K.; Lee, J. S.; Shin, J. H.; Moon, S. C.; Jung, B. H.; Kim, H. S.; Yu, B. S. *Bull. Korean Chem. Soc.* **2000**, *21*, 264–266.
(31) Caughey, W. S.; Raymond, L. D.; Horiuchi, M.; Caughey, B. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 12117–12122.
(32) Batinic-Haberle, I.; Spasojevic, I.; Stevens, R. D.; Bondurant, B.; Okado-Matsumoto, A.; Fridovich, I.; Vujaskovic, Z.; Dewhirst, M. W. *Dalton Trans.* **2006**, 617–624.
(33) Lambrechts, S. A. G.; Aalders, M. C. G.; Van Marle, J. *Antimicrob. Agents Chemother.* **2005**, *49*, 2026–2034.
(34) Malatesti, N.; Smith, K.; Savoie, H.; Greenman, J.; Boyle, R. W. *Int. J. Oncol.* **2006**, *28*, 1561–1569.
(35) (a) Meng, G. Z. G.; James, B. R.; Skov, K. A. *Can. J. Chem.* **1994**, *72*, 1894–1909. (b) Meng, G. G.; James, B. R.; Skov, K. A.; Korbelik, M. *Can. J. Chem.* **1994**, *72*, 2447–2457.
(36) Mayer-Gall, T.; Birkner, A.; Dyker, G. *J. Organomet. Chem.* **2008**, *693*, 1–3.
(37) (a) Yamamura, T. *Chem. Lett.* **1977**, 773–776. (b) Guilard, R.; Senglet, N.; Liu, Y. H.; Sazou, D.; Findsen, E.; Faure, D.; Des Courieres, T.; Kadish, K. M. *Inorg. Chem.* **1991**, *30*, 1898–1905.
(38) Matile, S.; Berova, N.; Nakanishi, K. *Chem. Biol.* **1996**, *3*, 379–392.
(39) Lee, S. J.; Hupp, J. T. *Coord. Chem. Rev.* **2006**, *250*, 1710–1723.
(40) Fleischer, E. B.; Shachter, A. M. *J. Heterocycl. Chem.* **1991**, *28*, 1693–1699.
(41) Fleischer, E. B.; Shachter, A. M. *Inorg. Chem.* **1991**, *30*, 3763–3769.
(42) Gerasimchuk, N. N.; Mokhir, A. A.; Rodgers, K. R. *Inorg. Chem.* **1998**, *37*, 5641–5650.
(43) Choi, M. S.; Yamazaki, T.; Yamazaki, I.; Aida, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 150–158.
(44) Bogatskii, A. V.; Zhilina, Z. I.; Vodzinskii, S. V.; Zakharova, R. M. *Russ. J. Org. Chem.* **1985**, *21*, 649–652.
(45) Malinka, E. A.; Khutornoi, A. M.; Vodzinskii, S. V.; Zhilina, Z. I.; Kamalov, G. L. *React. Kinet. Catal. Lett.* **1988**, *36*, 407–410.
(46) Malinka, E. A.; Kamalov, G. L.; Vodzinskii, S. V.; Melnik, V. I.; Zhilina, Z. I. *J. Photochem. Photobiol. A: Chem.* **1995**, *90*, 153–158.
(47) Stibrany, R. T.; Vasudevan, J.; Knapp, S.; Potenza, J. A.; Emge, T.; Schugar, H. J. *J. Am. Chem. Soc.* **1996**, *118*, 3980–3981.
(48) Rucareanu, S.; Mongin, O.; Schuwey, A.; Hoyler, N.; Gossauer, A.; Amrein, W.; Hediger, H.-U. *J. Org. Chem.* **2001**, *66*, 4973–4988.
(49) Tomohiro, Y.; Satake, A.; Kobuke, Y. *J. Org. Chem.* **2001**, *66*, 8442–8446.
(50) Rusakova, N. V.; Korovin, Y. V.; Zhilina, Z. I.; Vodzinskii, S. V.; Ishkov, Y. V. *J. Appl. Spectrosc.* **2004**, *71*, 504–511.
(51) Fukuda, S.; Satake, A.; Kobuke, Y. *Thin Solid Films* **2006**, *499*, 263–268.
(52) Kitagishi, H.; Satake, A.; Kobuke, Y. *Inorg. Chem.* **2004**, *43*, 3394–3405.
(53) Dogutan, D. K.; Zaidi, S. H. H.; Thamyongkit, P.; Lindsey, J. S. *J. Org. Chem.* **2007**, *72*, 7701–7714.
(54) Woodford, J. N.; Lindsey, J. S. *Inorg. Chem.* **1995**, *34*, 1063–1069.
(55) Laha, J. K.; Dhanalekshmi, S.; Taniguchi, M.; Ambroise, A.; Lindsey, J. S. *Org. Process Res. Dev.* **2003**, *7*, 799–812.
(56) Wickramasinghe, A.; Jaquinod, L.; Nurco, D. J.; Smith, K. M. *Tetrahedron* **2001**, *57*, 4261–4269.
(57) Balakumar, A.; Muthukumaran, K.; Lindsey, J. S. *J. Org. Chem.* **2004**, *69*, 5112–5115.
(58) Trova, M. P.; Gauuan, P. J. F.; Pechulis, A. D.; Bubb, S. M.; Bocckino, S. B.; Crapo, J. D.; Day, B. J. *Bioorg. Med. Chem.* **2003**, *11*, 2695–2707.

CHART 1



used to prepare dipyrromethanes **4d** and **4e**. The new compound **4m** was prepared in 89% yield by condensation of 1-methylsulfonylpyrrole-2-carboxaldehyde[60] with pyrrole in the presence of $InCl_3$. All of the dipyrromethanes shown in Chart 1 with the exception of **4c** and **4n** were acylated; the latter were employed in exploration of alternative routes to porphyrins (see Supporting Information).

Acylation can be carried out by treatment at −78 °C of the dipyrromethane-Grignard reagent with an *S*-2-pyridyl thioate (Mukaiyama reagent) or acid chloride.[61] The Mukaiyama reagents (**5a**−**k**) required for the target 1-acyldipyrromethanes were prepared by reaction of the corresponding acid chloride with 2-mercaptopyridine. Mukaiyama reagents **5a**,[53] **5b**,[61] **5h**,[61] and **5i**[61] are known; **5c**,[61] **5d**,[62] **5g**,[12] and **5k**[63] also are known and were prepared according to a new procedure. Formylation can be achieved by treatment of the dipyrromethane-Grignard reagent with phenyl formate[64] or by use of the Vilsmeier reagent. The Mukaiyama reagents and other acylating species [acid chloride **5l**, phenyl formate (**5m**), Vilsmeier reagent (**5n**)] are shown in Table 1.

Five major sets of 1-acyldipyrromethanes were prepared following the benchmark compound (**6a**),[53] which contained *p*-*tert*-butylphenyl at the 5-position and *p*-ethylphenyl at the 1-acyl site. The first set (**6b**−**j**) contained a *p*-tolyl group at the 5-position and diverse groups at the 1-acyl moiety. The second set (**6k**−**p**) contained pyridyl groups at both positions. The third set (**6r**−**u**) contained alkyl groups at both positions. The fourth set (**6j**, **6v**−**z**) contained the 1-formyl moiety and diverse 5-substituents. A final type of 1-acyldipyrromethane that we sought contained both alkyl and heterocyclic groups (**6q**), but this compound was not obtained in pure form. Of these 26 1-acyldipyrromethanes (Table 1), a handful are known compounds (**6a**,[53] **6g**,[12] **6j′**,[65] **6r**[65]).

The general procedures for preparing 1-acyldipyrromethanes worked well for most cases, though **6d**, **6f**, and **6k** required additional purification, and the 5-(pyridyl)-containing 1-acyldipyrromethanes gave slightly lower yields. Attempted acylation of 5-(2-pyridyl)dipyrromethane **4j** using the *p*-pyridyl-containing Mukaiyama reagent **5f** failed (starting material was recovered), whereas acylation of **4j** with *o*-pyridyl-containing Mukaiyama reagent **5e** provided the 1-acyldipyrromethane **6k** in 33% yield. Synthesis of a 1-mesitoyldipyrromethane (**6i**) was done by utilizing mesitoyl chloride (entry 9). In several cases (**6b** and **6c**) a boron complexation strategy[65] was employed to facilitate purification of the 1-acyldipyrromethane (see Supporting Information). Formylation of 5-(2-pyridyl)dipyrromethane **4j** via the Grignard conditions afforded recovered starting material; Vilsmeier conditions ($POCl_3$/DMF) afforded only a trace amount of product. Vilsmeier formylation of dipyrromethane **4i** afforded **6y** in 58% yield. We note that a number of the 1-acyldipyrromethanes are elaborate compounds containing three or four distinct nitrogenous heterocycles.

2. Conditions for the 1-Acyldipyrromethane Condensation. The development of the conditions for use in the condensation of a 1-acyldipyrromethane entailed an extensive exploration of metal reagents, solvents, bases, concentrations and molar ratios, and reaction duration. The standard procedure that emerged from this study entails reaction of a 1-acyldipyrromethane (100 mM) in the presence of $MgBr_2$ (3.0 mol equiv) and DBU (10.0 mol equiv) in toluene (115 °C) with stirring exposed to air for 12−14 h to give the target *trans*-A_2B_2-porphyrin. Such conditions were tested with substrates that are especially prone to acidolytic scrambling (e.g., **6a**, which bears *p*-*tert*-butylphenyl and *p*-ethylphenyl groups), and no scrambling was detected. The results from this survey are listed in Supporting Information. Three pertinent points deserve emphasis:

(1) The yield of porphyrin **Mg-1a** upon reaction of **6a** was 47%, 69%, and 65% at 50, 100, and 200 mM, respectively, but only 7% in the absence of toluene. The good yield at 200 mM augurs well for scale-up applications.

(2) Among a number of metals examined in place of $MgBr_2$, only $Pd(CH_3CN)_2Cl_2$ afforded a significant amount of the corresponding metalloporphyrin (37% yield).

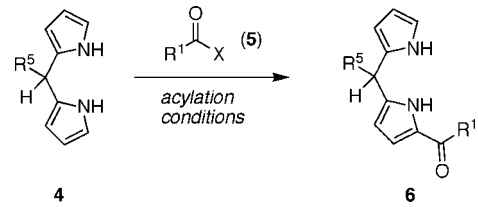
(3) The rationale for the exposure of the reaction mixture to air stems from the fact that the conversion of two 1-acyldipyrromethane molecules to a molecule of porphyrin requires an oxidant. The balanced reaction is shown in eq 1.

$$\mathbf{6a} + \mathbf{6a} + MgBr_2 \rightarrow \mathbf{Mg\text{-}1a} + 2HBr + 2H_2O + 2e^- + 2H^+ \quad (1)$$

Oxygen present in air would seem a likely source for the oxidizing equivalents, although prior studies of related reactions,

(59) Bhaumik, J.; Yao, Z.; Borbas, K. E.; Taniguchi, M.; Lindsey, J. S. *J. Org. Chem.* **2006**, *71*, 8807–8817.
(60) Abell, A. D.; Nabbs, B. K.; Battersby, A. R. *J. Am. Chem. Soc.* **1998**, *120*, 1741–1746.
(61) Zaidi, S. H. H.; Muthukumaran, K.; Tamaru, S.-I.; Lindsey, J. S. *J. Org. Chem.* **2004**, *69*, 8356–8365.
(62) Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1977**, *60*, 2860–2865.
(63) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *Tetrahedron* **1991**, *47*, 7897–7910.
(64) Ptaszek, M.; McDowell, B. E.; Lindsey, J. S. *J. Org. Chem.* **2006**, *71*, 4328–4331.
(65) Muthukumaran, K.; Ptaszek, M.; Noll, B.; Scheidt, W. R.; Lindsey, J. S. *J. Org. Chem.* **2004**, *69*, 5354–5364.

TABLE 1. Synthesis of 1-Acyldipyrromethanes[a]



4 6

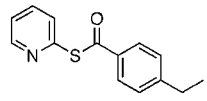
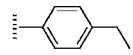
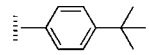
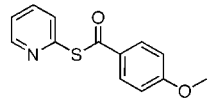
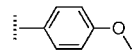
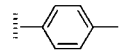
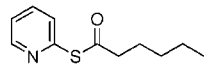
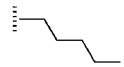
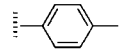
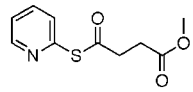
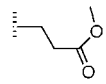
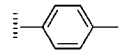
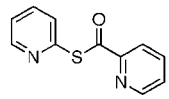
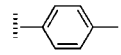
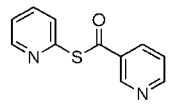
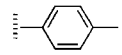
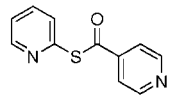
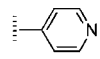
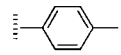
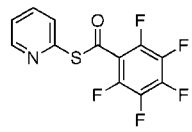
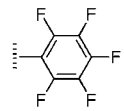
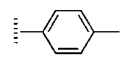
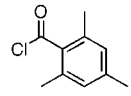
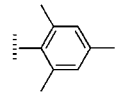
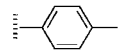
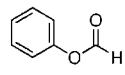
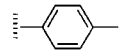
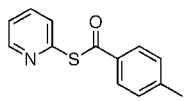
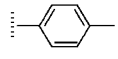
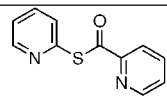
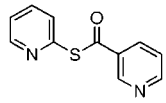
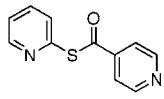
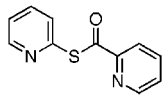
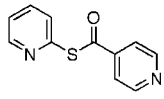
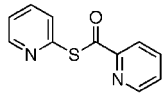
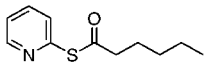
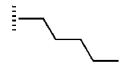
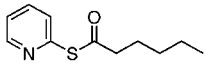
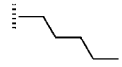
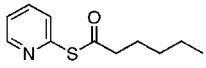
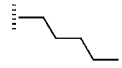
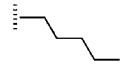
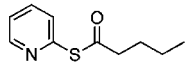
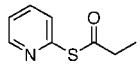
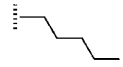
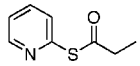
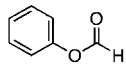
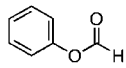
Entry	4	Acylating reagent		1-Acyldipyrromethane			
		Structure	Cmpd	R^1	R^5	Cmpd	Yield (%)
1	**4a**		**5a**			**6a**	66[b]
2	**4b**		**5b**			**6b**	37[c]
3	**4b**		**5c**			**6c**	22[c]
4	**4b**		**5d**			**6d**	20
5	**4b**		**5e**			**6e**	76
6	**4b**		**5f**			**6f**	61
7	**4b**		**5g**			**6g**	75[d]
8	**4b**		**5h**			**6h**	79
9	**4b**		**5l**			**6i**	27
10	**4b**		**5m**			**6j**	41
11	**4g**		**5i**			**6j′**	62[e]

TABLE 1. Continued

Entry	4	Acylating reagent		1-Acyldipyrromethane			
		Structure	Cmpd	R^1	R^5	Cmpd	Yield (%)
12	**4j**		**5e**			**6k**	33
13	**4k**		**5f**			**6l**	34
14	**4l**		**5g**			**6m**	60
15	**4k**		**5e**			**6n**	47
16	**4k**		**5g**			**6o**	29
17	**4l**		**5e**			**6p**	51
18	**4l**		**5c**			**6q**	---[f]
19	**4m**		**5c**			---	---[g]
20	**4f**		**5c**			**6r**	63[h]
21	**4e**		**5j**			**6s**	46
22	**4f**		**5k**			**6t**	67
23	**4d**		**5k**			**6u**	81
24	**4k**		**5m**			**6v**	37
25	**4l**		**5m**			**6w**	49
26	**4h**		**5m**			**6x**	65[i]
27	**4i**	Vilsmeier reagent	**5n**			**6y**	58
28	**4g**	Vilsmeier reagent	**5n**			**6z**	46[j]

[a] The acylation reactions were carried out with 5−15 mmol of reactants unless noted otherwise in the experimental section. [b] Reference 53. [c] Yield is given after two steps (boron complexation and decomplexation). [d] Reference 12. [e] Reference 65. [f] Could not be purified. [g] Multiple products on the basis of TLC and ^{1}H NMR analyses. [h] Reference 65. [i] Reference 64. [j] Reference 8.

which were quite limited in methods and in range of substrates examined, were not conclusive.[5,8,53]

3. Rational Synthesis of *trans*-A_2B_2-Porphyrins. Conventional Heating. The standard conditions were applied to a wide variety of 1-acyldipyrromethanes to prepare the corresponding *trans*-A_2B_2-porphyrins. Each reaction was carried out with 100 mM 1-acyldipyrromethane and a scale ranging from 0.2 to 3.8 mmol. In each successful porphyrin synthesis, TLC analysis (silica, CH_2Cl_2) of the crude reaction mixture revealed the presence of a trace amount of free base porphyrin (close to the solvent front), the desired magnesium porphyrin, and a trace amount of unreacted 1-acyldipyrromethane. The results are shown in Table 2.

The reaction of 1-acyldipyrromethane **6a**, which was used in all of the studies to develop conditions, gave the highest yield of porphyrin (**Mg-1a** in 69% yield; entry 1, Table 2). Most members of each set of 1-acyldipyrromethanes shown in Table 1 were examined for conversion to the corresponding *trans*-A_2B_2-porphyrin. The set of 5-*p*-tolyl-1-acyldipyrromethanes (**6b**−**j**) enabled identification of the effects of a particular substituent. In general, 1-acyldipyrromethanes that possess electron-releasing aryl substituents resulted in porphyrins (**Mg-1a**, **Mg-1b**, **Mg-1c**) in relatively high yields. 1-Acyldipyrromethanes bearing a pyridyl substituent (*o*-, *m*-, *p*-) afforded dipyridyl porphyrins **Mg-1e**, **Mg-1f**, and **Mg-1g** in 6%, 43%, and 25% yield, respectively, upon use of larger excesses of $MgBr_2$ and DBU. **Mg-1f** and **Mg-1g** exhibited poor solubility yet were purified by simply washing the crude reaction mixture with methanol. 1-Formyldipyrromethane **6j** gave the corresponding *trans*-A_2-porphyrin **Mg-1j** in 39% yield (90% purity owing to the presence of the chlorin analogue).

A sizable number of attempted reactions did not give the corresponding porphyrin. One surprise was the failure of a 1-acyldipyrromethane lacking a *meso* substituent (**6j′**) given the excellent results with the transposed analogue **6j**. The presence of a bulky group (pentafluorophenyl, mesityl) at the 1-acyl position resulted in little (**Mg-1h**) or no porphyrin (**Mg-1i**). The 1-acyldipyrromethanes bearing two pyridyl groups or two alkyl groups also afforded little or no porphyrin. Further failures include 1-formyldipyrromethanes bearing a pyridyl, acetal, or ester group at the 5-position. These studies indicated only modest scope for macrocycle formation under conventional heating and prompted a parallel set of studies of the reactions carried out with microwave heating.

Microwave Heating. Microwave-assisted organic reactions have become popular for the synthesis of numerous classes of compounds.[66] We previously found that porphine can be synthesized efficiently under microwave irradition.[8] Initially, we investigated microwave-assisted reactions under the standard conditions (toluene, 100 mM of the 1-acyldipyrromethane, 3 mol equiv of $MgBr_2$ and 10 mol equiv of DBU) for the trials shown in Table 2 where poor yields were obtained with conventional heating. The microwave reactions were carried out for ∼2 h versus 12−14 h for the conventional reactions. In some cases, no improvement was observed (entries 5, 8−10, and 16−18). On the other hand, a substantial increase in yield was observed in several cases, including *trans*-A_2-porphyrin **1y** (A = ethoxycarbonyl) and three porphyrins each bearing four pyridyl groups. The latter include two A_4-porphyrins (tetra-*p*-pyridylporphyrin **Mg-1m** and tetra-*m*-pyridylporphyrin **Mg-1l**) and a *trans*-A_2B_2-porphyrin bearing two *p*-pyridyl and two *m*-pyridyl groups (**Mg-1o**). The porphyrins were obtained in 21−61% yields (Table 2, entries 12−14). These results indicate the utility of this approach for the synthesis of porphyrins bearing four heterocyclic substituents. Although demonstrated in part by the preparation of A_4-porphyrins, these promising results encouraged further study of the scope of microwave-assisted porphyrin syntheses (vide infra).

4. Statistical Synthesis of *meso*-Substituted Porphyrins from 1-Acyldipyrromethanes. 1. Approach. A time-honored statistical synthesis in porphyrin chemistry entails reaction of two aldehydes (A, B) with pyrrole, affording a mixture of six porphyrins (A_4, A_3B, *trans*-A_2B_2, *cis*-A_2B_2, AB_3, B_4). In such mixtures, the separation of the A_3B-porphyrin is often quite straightforward for those cases where the substituents in aldehydes A and B have different polarity.[67] However, the separation of *cis*-A_2B_2- and *trans*-A_2B_2-porphyrins is often exceptionally difficult. By contrast, the condensation of two nonidentical 1-acyldipyrromethanes would at most yield only three porphyrins, which presents a more tractable separation problem. Two sets of condensations were examined under microwave irradiation with a particular focus on those substituents that are difficult to introduce via other procedures, particularly heterocyclic moieties, alkyl chains or no substituents (H).

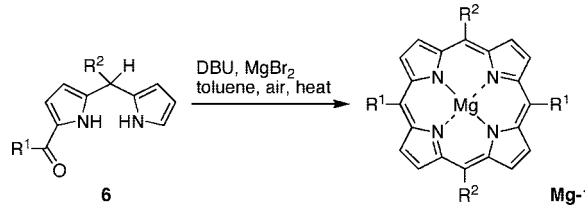
Route to *cis*-AB-, *cis*-A_2-, or A-Porphyrins. Reaction of 1-formyldipyrromethane and an AB-substituted 1-acyldipyrromethane is expected to afford a mixture composed of porphine, the *trans*-A_2B_2-porphyrin, and the hybrid *cis*-AB-porphyrin. Note that no *trans*-AB-porphyrin can form, which would complicate separation of the target *cis*-AB-porphyrin. When A = B, the hybrid porphyrin contains the *cis*-A_2 substitution pattern. Access to each of these architectures was explored with 1-acyldipyrromethanes that contained two heterocycles (**6k**, **6l**, **6m**, **6n**, **6o**, and **6p**). Each 1-acyldipyrromethane was condensed with 1-formyldipyrromethane (**6z**). As one example, the reaction of 1-acyldipyrromethane **6m** (bearing two *p*-pyridyl groups) with 1-formyldipyrromethane followed by treatment with TFA to demetalate the magnesium chelates afforded the three free base porphyrins: *meso*-tetrapyridylporphyrin (**1m**, 14%), porphine (16%), and the hybrid *cis*-A_2-porphyrin bearing the two pyridyl units (**2c**, 27%). TLC analysis showed the three free base porphyrins to be widely separated. Column chromatographic separation afforded the three porphyrins, which upon washing with hexanes and methanol yielded the pure porphyrin as a purple powder. In this manner, the target *cis*-AB- and *cis*-A_2-porphyrins were obtained in 9−28% yield (Table 3, entries 1−5), each of which contains two heterocyclic substituents.

When the 1-acyldipyrromethane contains only one substituent (A) and is condensed with 1-formyldipyrromethane, the expected porphyrins are the *trans*-A_2-porphyrin, porphine, and the hybrid A-porphyrin, which contains a single *meso* substituent. Access to such A-porphyrins was explored with 1-formyldipyrromethanes that contained one heterocycle at the 5-position (**6v**, **6w**). In this manner, two A-porphyrins were obtained (Table 3, entries 7 and 8; 32% and 21% yields), each of which contains a single pyridyl substituent. It is noteworthy that relatively few porphyrins have been prepared that contain one or two pyridyl groups and no other substituents.[18,68–70]

(66) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.

(67) Lindsey, J. S. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 1, pp 45−118..

TABLE 2. ***trans*-A_2B_2-Magnesium Porphyrin Synthesis Directly from 1-Acyldipyrromethanes**[a]



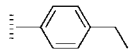
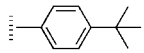
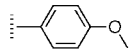
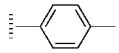
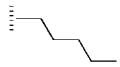
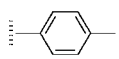
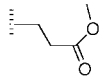
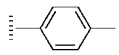
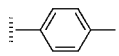
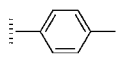
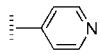
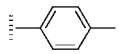
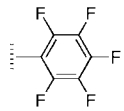
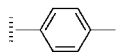
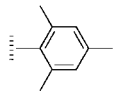
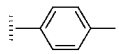
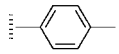
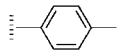
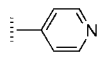
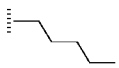
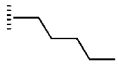
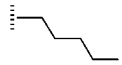
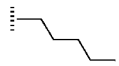
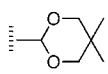
Entry	1-Acyldipyrromethane			Porphyrin Synthesis			Porphyrin Type
				Conventional Heating		Microwave Irradiation	
	Cmpd	R^1 (acyl)	R^2 (meso)	Cmpd	Yield (%)	Yield (%)	
1	**6a**			**Mg-1a**	69	NA[b]	*trans*-A_2B_2
2	**6b**			**Mg-1b**	46	NA	*trans*-A_2B_2
3	**6c**			**Mg-1c**	31	NA	*trans*-A_2B_2
4	**6d**			**Mg-1d**	Trace	NA	*trans*-A_2B_2
5	**6e**			**Mg-1e**	6[c]	Trace	*trans*-A_2B_2
6	**6f**			**Mg-1f**	43[d]	NA	*trans*-A_2B_2
7	**6g**			**Mg-1g**	25[e]	NA	*trans*-A_2B_2
8	**6h**			**Mg-1h**	2[f]	1	*trans*-A_2B_2
9	**6i**			**Mg-1i**	0	0	*trans*-A_2B_2
10	**6j**			**Mg-1j**	39	19[g]	*trans*-A_2
11	**6j′**			**Mg-1j**	Trace	0	*trans*-A_2
12	**6l**			**Mg-1l**	Trace	61	A_4
13	**6m**			**Mg-1m**	Trace	47	A_4
14	**6o**			**Mg-1o**	3[f]	21	*trans*-A_2B_2
15	**6q**			**Mg-1q**	Trace	NA	*trans*-A_2B_2

TABLE 2. Continued

Entry	1-Acyldipyrromethane			Porphyrin Synthesis			Porphyrin Type
				Conventional Heating		Microwave Irradiation	
	Cmpd	R^1 (acyl)	R^2 (meso)	Cmpd	Yield (%)	Yield (%)	
16	**6r**			**Mg-1r**	NA	0	A_4
17	**6s**			**Mg-1s**	NA	0	*trans*-A_2B_2
18	**6t**			**Mg-1t**	0	0	*trans*-A_2B_2
19	**6u**			**Mg-1u**	NA	0	A_4
20	**6v**			**Mg-1v**	Trace	4	*trans*-A_2
21	**6x**			**Mg-1x**	Trace	NA	*trans*-A_2
22	**6y**			**1y**[g]	0	13	*trans*-A_2
23	**6z**			**Mg-porphine**	40[h]	37[h]	--

[a] The reactions were carried out with 0.1−2.3 mmol of 1-acyldipyrromethane unless noted otherwise. [b] NA = not attempted. [c] 9 equiv of $MgBr_2$, 35 equiv of DBU. [d] 3 equiv of $MgBr_2$, 20 equiv of DBU. [e] 6 equiv of $MgBr_2$, 10 equiv of DBU. [f] The yield was determined by absorption spectrometry. [g] The free base porphyrin obtained by demetalation. [h] Reference 8.

Route to *cis*-ABC_2- or *cis*-A_2B_2-Porphyrins. Amphipathic porphyrins are of interest for organization in monolayers and in lipid bilayers.[71] We sought to exploit the present methodology to prepare *cis*-A_2B_2-porphyrins bearing two pyridyl groups and two pentyl groups. To our knowledge, only one example has been reported of a *cis*-A_2B_2-porphyrin bearing pyridyl/alkyl groups at the *meso* positions.[44] Thus, a series of reactions was carried out where the 1-acyldipyrromethane bearing two pentyl substituents (**6r**) was condensed with a 1-acyldipyrromethane bearing two pyridyl substituents. The resulting reactions potentially afford *meso*-tetrapentylporphyrin, the *meso*-tetrapyridylporphyrin (A_4 or *trans*-A_2B_2), and the hybrid *cis*-A_2B_2- or *cis*-ABC_2-porphyrin. The results are summarized in Table 4. In each case examined, the hybrid porphyrin was obtained in yields of 7−26%, the tetrapyridylporphyrin was obtained in yields of 5−23%, and no *meso*-tetrapentylporphyrin was isolated; the two porphyrins that were isolated were widely separated upon chromatography (see Supporting Information). The failure to obtain the tetraalkylporphyrin was not unexpected given that the condensation alone of the dipentyl 1-acyldipyrromethane **6r** also fails altogether (Table 2, entry 16). In this regard, the successful synthesis of the hybrid porphyrin is remarkable.

In summary, this study shows that statistical condensation of 1-acyldipyrromethanes under microwave irradiation can provide entrée into a class of porphyrins having limited access with the current procedures (*cis*-ABC_2, *cis*-A_2B_2, *cis*-AB, and A). The *cis*-substituted porphyrins are obtained without accompaniment by the *trans* isomer, thereby facilitating purification.

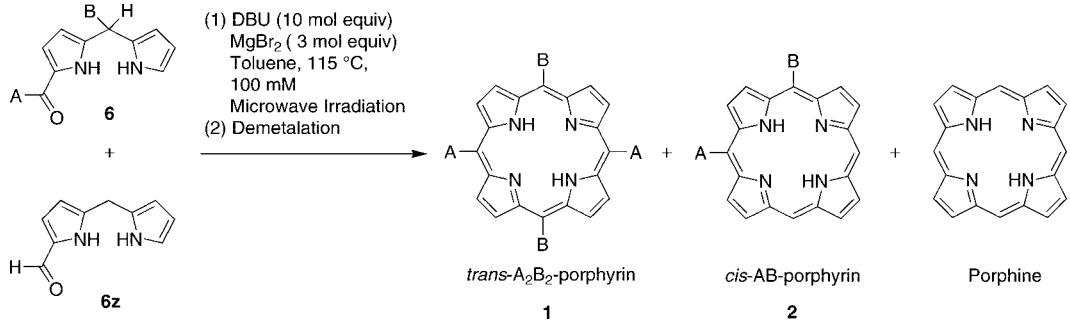
Amphipathic Porphyrin. To accentuate the amphipathic character of the dipyridyl/dipentylporphyrins, one such porphyrin (**3c**) was treated with excess methyl iodide to form the quaternized product containing methyl pyridinium units (Scheme 2). The bis-quaternized porphyrin (**3c-Me_2I_2**) was isolated in 90% yield simply by washing with hexanes. Porphyrin **3c-Me_2I_2** contains two pentyl groups in a *cis*-configuration and two methyl pyridinium groups in a *cis*-configuration, which provides an attractive amphipathic architecture for examination in bilayer lipid membranes. The synthetic route employed here is more versatile than a prior route to *cis*-A_2B_2-porphyrins that were designed for studies of bilayer lipid membranes.[71]

Outlook

The nonacidic, magnesium-mediated conditions described here provide access to diverse *meso*-substituted porphyrins via the condensation of two 1-acyldipyrromethane molecules. The nonacidic nature of the conditions sidesteps acidolytic processes

(68) Tsuda, A.; Nakamura, T.; Sakamoto, S.; Yamaguchi, K.; Osuka, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2817–2821.
(69) Hwang, I. W.; Kamada, T.; Ahn, T. K.; Ko, D. M.; Nakamura, T.; Tsuda, A.; Osuka, A.; Kim, D. *J. Am. Chem. Soc.* **2004**, *126*, 16187–16198.
(70) Yao, M.; Iwamura, Y.; Inoue, H.; Yoshioka, N. *Langmuir* **2005**, *21*, 595–601.
(71) Hwang, K. C.; Mauzerall, D.; Wagner, R. W.; Lindsey, J. S. *Photochem. Photobiol.* **1994**, *59*, 145–151.

TABLE 3. Statistical *cis*-AB-Porphyrin Synthesis from Two Nonidentical 1-Acyldipyrromethanes[a]



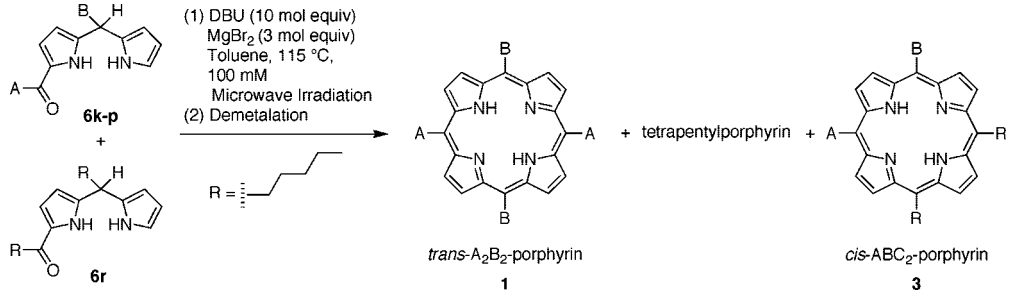
Entry	1-Acyldipyrromethane			Porphyrin **2**	Yield (%)	Porphyrin **1**	Yield (%)	Porphyrin	Yield (%)
	Cmpd	A (acyl)	B (meso)						
1	**6k**			**2a**	13	**1k**	12	Porphine	15
2	**6l**			**2b**	28	**1l**	3	Porphine	13
3[b]	**6m**			**2c**	27	**1m**	14	Porphine	16
4	**6n**			**2d**	9	**1n**	11	Porphine	7
5[c]	**6o**			**2e**	14	**1o**	NI	Porphine	NI
6	**6p**			**2f**	0	**1p**	11	Porphine	28
7	**6v**			**2g**	32	**1v**	Trace	Porphine	6
8	**6w**			**2h**	21	**1w**	11	Porphine	trace

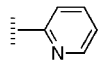
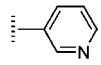
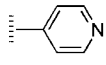
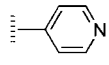
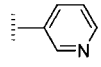
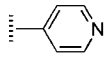
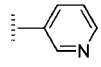
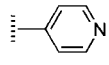
[a] All reactions were carried out under microwave irradiation with 0.2 mmol of 1-acyldipyrromethane unless noted otherwise. The porphyrin was purified by column chromatography followed by washing with hexanes. [b] 0.1 mmol of 1-acyldipyrromethane was used. [c] NI = not isolated.

and enables the use of 1-acyldipyrromethanes that bear pyridyl or alkyl substituents. Pyridyl substituents have been some of the most sought after substituents yet also the most challenging owing to their facile acid-complexation behavior. The present method thus complements the methods shown in Scheme 1 for gaining access to *trans*-A_2B_2- or *trans*-A_2-porphyrins via acid-catalyzed processes (routes I, IIa, IIb, and III). The conditions explored here for the reaction of a 1-acyldipyrromethane are more general than those in route IIc, which requires an expensive palladium reagent and affords the corresponding palladium porphyrin.

Much about mechanism remains unknown. The conversion of two 1-acyldipyrromethanes to the porphyrin entails, in unknown order, formation of two C−C bonds, elimination of two molecules of water, dehydrogenation (with an unknown oxidant), and metal complexation. The good yield at 100 or 200 mM reactions tends to suggest the formation of a magnesium complex with the two 1-acyldipyrromethanes early in the process, thereby favoring intramolecular over intermolecular reaction (i.e., cyclization over polymerization). The 1-acyldipyrromethanes containing an *o*-pyridyl group (but not *m*- or *p*-pyridyl) at the acyl site gave low yields of porphyrin, which may stem from competitive coordination of magnesium by the *o*-pyridyl and keto functional groups. Although early complexation with magnesium would seem reasonable, magnesium insertion into free base porphyrins is facile under these and analogous[54] reaction conditions; thus, the isolation of the magnesium porphyrin alone is not sufficient proof of a templated reaction process (see Supporting Information). Concerning the course of reaction, it should be noted that each 1-acyldipyrromethane that bears a 5-substituent presumably exists as a pair of enantiomers; the resulting intermediate(s) on the path to porphyrin may be diastereomeric with different reactivities. While studies to investigate these issues are beyond the scope of the present work, it deserves noting that attempts to apply these conditions to the reaction of a 1,9-diacyldipyrromethane and a dipyrromethane gave only a trace of the corresponding porphyrin. On the other hand, the condensation of 5-phenyldipyrromethane and *p*-tolualdehyde gave the *trans*-A_2B_2-porphyrin in 20% yield, but yields upon extension to other substrates were quite low (see Supporting Information). Thus, at present the basic, magnesium-mediated reaction conditions

TABLE 4. Statistical *cis*-ABC_2-Porphyrin Synthesis from Two Nonidentical 1-Acyldipyrromethanes[a]



Entry	AB-1-Acyldipyrromethane			Porphyrin **3**	Yield (%)	Porphyrin **1**	Yield (%)
	Cmpd	A (acyl)	B (meso)				
1	**6k**			**3a**[b]	7	**1k**[c]	10
2	**6l**			**3b**[b]	17	**1l**[c]	23
3	**6m**			**3c**[b]	26	**1m**[c]	12
4	**6n**			**3d**	12	**1n**	14
5	**6o**			**3e**	16	**1o**	5
6	**6p**			**3f**	22	**1p**	15

[a] All reactions were carried out under microwave irradiation with 0.2 mmol of each 1-acyldipyrromethane unless noted otherwise. Each porphyrin was purified by column chromatography followed by washing with hexanes. [b] *cis*-A_2B_2-porphyrin. [c] A_4-porphyrin.

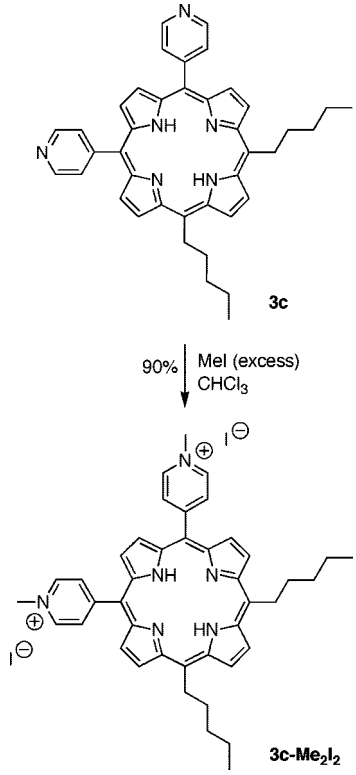
appear restricted to the condensation of 1-acyldipyrromethanes,[8] the cyclization of 1-acylbilanes,[53] and magnesium insertion into free base porphyrins.[54]

The statistical condensations described herein have afforded entrée into porphyrins with substituent patterns that previously presented difficulties (including *cis*-A_2B_2 and *cis*-ABC_2, and the sparsely substituted analogues *cis*-A_2, *cis*-AB, A), do so in each case without concomitant formation of the *trans* isomer, and are compatible with pyridyl and alkyl substituents. Statistical condensations have long been used in porphyrin chemistry to access a desired porphyrin architecture, typically by chromatographic separation of the resulting mixture of porphyrins.[67] The most prevalent statistical routes to porphyrins include (i) two aldehydes and pyrrole to give six porphyrins;[67] (ii) two aldehydes and a dipyrromethane (or vice versa) to give three porphyrins;[67] (iii) two dipyrromethane-1-carbinols to give three porphyrins;[72] (iv) one aldehyde, 2-hydroxymethylpyrrole, and a dipyrromethane to give two porphyrins;[73] and (v) one aldehyde, pyrrole, and tripyrrane to give two porphyrins.[73] All of the methods that employ dipyrromethanes or tripyrranes (ii−v) also employ acid catalysis conditions, which may give poor results with pyridyl or alkyl groups.

Given the widespread acceptance of statistical routes in porphyrin synthesis, it is surprising that few efforts other than the pioneering work of Drain,[74–76] Richert,[77–79] and Boyle[80,81] have been made toward the exploitation of such routes in the development of porphyrin libraries. The routes that have been examined rely on (1) the reaction of a collection of aldehydes with pyrrole,[74,77,78,82] (2) derivatization of a pure porphyrin,[75,76,79,83,84] or (3) derivatization of a mixture of porphyrins.[74,78] Few combinatorial ap-

(72) Wallace, D. M.; Leung, S. H.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1993**, *58*, 7245–7257.
(73) Ryppa, C.; Senge, M. O.; Hatscher, S. S.; Kleinpeter, E.; Wacker, P.; Schilde, U.; Wiehe, A. *Chem. Eur. J.* **2005**, *11*, 3427–3442.
(74) Drain, C. M.; Gong, X. C.; Ruta, V.; Soll, C. E.; Chicoineau, P. F. *J. Comb. Chem.* **1999**, *1*, 286–290.
(75) Chen, X.; Hui, L.; Foster, D. A.; Drain, C. M. *Biochemistry* **2004**, *43*, 10918–10929.
(76) Samaroo, D.; Vinodu, M.; Chen, X.; Drain, C. M. *J. Comb. Chem.* **2007**, *9*, 998–1011.
(77) Berlin, K.; Jain, R. K.; Tetzlaff, C.; Steinbeck, C.; Richert, C. *Chem. Biol.* **1997**, *4*, 63–77.
(78) Berlin, K.; Jain, R. K.; Richert, C. *Biotechnol. Bioeng.* **1998**, *61*, 107–118.
(79) Dombi, K. L.; Richert, C. *Molecules* **2000**, *5*, 1265–1280.
(80) Elgie, K. J.; Scobie, M.; Boyle, R. W. *Tetrahedron Lett.* **2000**, *41*, 2753–2757.
(81) Shi, B. L.; Scobie, M.; Boyle, R. W. *Tetrahedron Lett.* **2003**, *44*, 5083–5086.
(82) Fagadar-Cosma, E.; Cseh, L.; Badea, V.; Fagadar-Cosma, G.; Vlascici, D. *Comb. Chem. High Throughput Screening* **2007**, *10*, 466–472.
(83) Okuno, Y.; Ford, W. E.; Calvin, M. *Synthesis* **1980**, 537–539.

SCHEME 2



proaches have relied on routes that afford a more narrow set of porphyrins.[80,81] The condensation of 1-acyldipyrromethanes appears attractive in this latter regard for two reasons: (i) the ability to focus on selected architectures such as *cis*-A_2B_2-porphyrins, and (ii) the tolerance of the reaction conditions toward heterocyclic substituents. The ability to incorporate heterocyclic substituents in sparsely substituted architectures is of interest for a number of biomedical applications, where charged or amphipathic substituents are desired in a compact molecular design.

Experimental Section

Known Porphyrins. Metalloporphyrins **Mg-1e**,[42] **Mg-1m**,[85] and **Mg-porphine**[8] prepared herein are known, as are free base porphyrins **1b**,[86] **1e**,[42] **1f**,[17] **1g**,[12] **1h**,[87] **1j**,[88] **1k**,[89] **1l**,[90] **1m**,[91] **1r**,[92] **1v**,[23] **1w**,[18] **1y**,[58] **2c**,[18] and **2h**.[18]

Synthesis of Mukaiyama Reagents (Method 1).[61] A solution of 2-mercaptopyridine (5.55 g, 50.0 mmol) in THF (50.0 mL) was treated slowly with an acid chloride (50.0 mmol). The resulting slurry was stirred for 30 min. The precipitate was collected by filtration and washed with hexanes (70.0 mL) in a Buchner funnel. The filtered material was added into a biphasic solution of saturated aqueous $NaHCO_3$ (100 mL) and diethyl ether (100 mL). The mixture was stirred until the foaming subsided. The organic layer was removed, and the water layer was extracted with diethyl ether. The combined organic extract was dried (Na_2SO_4) and filtered. The filtrate was concentrated to give a solid, which was washed with hexanes (~20 mL) to afford the product.

***S*-2-Pyridyl Hexanothioate (5c).** Following Method 1, a solution of 2-mercaptopyridine (6.66 g, 60.0 mmol) in THF (60 mL) was treated with hexanoyl chloride (8.3 mL, 60 mmol) to afford a yellow liquid (12.2 g, 97%): ^{1}H NMR δ 0.89−0.91 (m, 3H), 1.31−1.34 (m, 4H), 1.70−1.74 (m, 2H), 2.69 (t, J = 7.6 Hz, 2H), 7.26−7.29 (m, 1H), 7.60− 7.62 (m, 1H), 7.71−7.76 (m, 1H), 8.61−8.62 (m, 1H); ^{13}C NMR δ 14.0, 22.5, 25.3, 31.2, 44.4, 123.7, 130.4, 137.4, 150.5, 151.7, 196.7; FAB-MS obsd 210.0958, calcd 210.0953 ($C_{11}H_{15}NOS$). Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 62.76; H, 7.19; N, 7.01.

Synthesis of 1-Acyldipyrromethanes (Method 2).[4] A solution of EtMgBr (38 mL, 38 mmol, 1.0 M in THF) was added slowly to a solution of the dipyrromethane (15.0 mmol) in THF (30.0 mL) under argon. The resulting mixture was stirred at room temperature for 10 min, and then cooled to −78 °C. A solution of Mukaiyama reagent (15.0 mmol) in THF (30.0 mL) was added to the reaction mixture. The solution was stirred at −78 °C for 10 min and then allowed to warm to room temperature. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate. The organic layer was washed (water, brine), dried (Na_2SO_4), and filtered. The filtrate was concentrated. The resulting product was chromatographed [silica, CH_2Cl_2 (until all the unreacted dipyrromethane was eluted) → hexanes/ethyl acetate (3:1)] to afford the corresponding 1-acyldipyrromethane.

5-(4-Methylphenyl)-1-picolyldipyrromethane (6e). Following Method 2, a solution of EtMgBr (38 mL, 38 mmol, 1.0 M in THF), 5-(4-methylphenyl)dipyrromethane (**4b**, 3.55 g, 15.0 mmol, in 30 mL of THF), and a solution of *S*-2-pyridyl picolinothioate (**5e**, 3.24 g, 15.0 mmol, in 30 mL of THF) afforded an oily product, which upon chromatography [silica, CH_2Cl_2/ethyl acetate (7:2), 4 cm dia × 30 cm] afforded a brown powder (3.91 g, 76%): mp 54 °C (dec); ^{1}H NMR δ 2.35 (s, 3H), 5.53 (s, 1H), 6.01−6.02 (m, 1H), 6.10−6.12 (m, 1H), 6.19−6.21 (m, 1H), 6.73−6.74 (m, 1H), 7.13− 7.18 (m, 4H), 7.39−7.42 (m, 2H), 7.82−7.86 (m, 2H), 8.02−8.12 (m, 1H), 8.17−8.18 (brs, 1H), 8.44−8.58 (brs, 1H); ^{13}C NMR δ 21.3, 44.2, 107.77, 107.78, 108.7, 110.8, 118.0, 124.1, 126.3, 128.6, 129.7, 131.7 (brs), 137.2, 137.5, 138.2, 141.6, 148.2, 155.7, 171.5; FAB-MS obsd 341.1528, calcd 341.1526. Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31. Found: C, 76.09; H, 5.77; N, 11.71. The elemental analysis data are consistent with the presence of one molecule of ethyl acetate per four molecules of product.

Synthesis of 1-Formyldipyrromethanes (Method 3).[64] A sample of dipyrromethane (15.0 mmol) in THF (30 mL) was treated with MesMgBr (30 mL, 30 mmol, 1.0 M in THF). After 10 min, the mixture was cooled to −78 °C. Phenyl formate (**5m**, 3.27 mL, 30.0 mmol) was added in one portion. The reaction mixture was stirred at −78 °C for 1 h. The cooling bath was removed, and stirring was continued for 1 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (~150 mL). The organic extract was washed (water, brine) and concentrated. The resulting oil was dissolved in CH_3CN (150 mL) and treated with 2 M aqueous NaOH (90 mL). The resulting mixture was stirred vigorously at room temperature for 1 h. Water (~100 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic phase was washed (saturated aqueous NH_4Cl, water, brine), dried (Na_2SO_4), and concentrated. The resulting dark oil was chromatographed [silica, CH_2Cl_2 → CH_2Cl_2/ethyl acetate (10:1)] to afford the product.

1-Formyl-5-(3-pyridyl)dipyrromethane (6v). Following Method 3, reaction of 5-(3-pyridyl)dipyrromethane (**4k**, 1.12 g, 5.00 mmol in 20 mL of THF), MesMgBr (10.0 mL, 10 mmol, 1.0 M in THF), and phenyl formate (**5m**, 1.1 mL, 10. mmol) afforded an oily product. Column chromatography (silica, ethyl acetate) afforded a pure product (an orange solid, 0.304 g) and mixed fractions; the latter were rechromatographed (silica, ethyl acetate) to afford an additional 0.162 g of product. Total yield (0.466 g, 37%): mp 174−176 °C (dec); ^{1}H NMR (300 MHz) (THF-d_8) δ 5.49 (s, 1H), 5.65−5.67 (m, 1H), 5.86−5.88 (m, 1H), 5.95−5.98 (m, 1H), 6.63−6.66 (m, 1H), 6.80−6.82 (m, 1H), 7.18−7.22 (m, 1H), 7.44−7.49 (m, 1H), 8.49−8.42 (m, 2H two signals overlapped),

(84) (a) Chaleix, V.; Sol, V.; Guilloton, M.; Granet, R.; Krausz, P. *Tetrahedron Lett.* **2004**, *45*, 5295–5299. (b) Biron, E.; Voyer, N. *Chem. Commun.* **2005**, 4652–4654. (c) Schroder, T.; Schmitz, K.; Niemeier, N.; Balaban, T. S.; Krug, H. F.; Schepers, U.; Brase, S. *Bioconjugate Chem.* **2007**, *18*, 342–354.
(85) O'Shea, D. F.; Miller, M. A.; Matsueda, H.; Lindsey, J. S. *Inorg. Chem.* **1996**, *35*, 7325–7338.

9.40 (s, 1H), 9.84−9.98 (br, 1H), 11.20−11.29 (brs, 1H); ^{13}C NMR (THF-d_8) δ 42.8, 108.4, 111.1, 118.7, 121.2, 124.0, 131.9, 134.6, 136.4, 138.7, 142.9, 149.1, 151.1, 178.8 (signals derived from two carbon atoms are apparently overlapped); ESI-MS obsd 252.1134, calcd 252.1131 [$(M + H)^+$, M = $C_{15}H_{13}N_3O$]. Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.58.; H, 5.21; N, 16.44.

Condensation of a 1-Acyldipyrromethane via Conventional Heating at 135 °C (Method 4A). A sample of 1-acyldipyrromethane (1.00 g) was placed in a 250 mL one-necked round-bottom flask that was oven-dried and contained a magnetic stir bar. A Teflon septum was attached, and toluene (∼10 to ∼25 mL) was added via syringe. The reaction mixture was stirred at room temperature for 1 min, whereupon DBU (10 mol equiv versus **6a**) was added dropwise via syringe under vigorous stirring. The resulting mixture was stirred at room temperature for 5 min. The mixture darkened. The septum was removed, and $MgBr_2$ (3.0 mol equiv versus **6a**) was added in one portion under vigorous stirring. (Note that a dry flask is essential, as is vigorous stirring, so that $MgBr_2$ does not clump as a solid on the bottom of the flask, which typically lowers the yield of porphyrin.) The septum was replaced, and the heterogeneous reaction mixture was stirred for 1 min at room temperature. The flask was fitted with a reflux condenser (4 cm dia × 30 cm) having the top end open to the atmosphere, and the flask was placed in an oil bath preheated to 135 °C. The reaction mixture was stirred under reflux. When porphyrin formation was complete (on the basis of TLC analysis and absorption spectroscopy, typically after overnight reaction), the crude reaction mixture was allowed to cool to room temperature and then concentrated. The resulting residue was dissolved in CH_2Cl_2 (2 mL) and filtered through a column [alumina, 500 g, 4 cm dia × 30 cm, CH_2Cl_2 → CH_2Cl_2/ethyl acetate (5:1 → 3:1), ∼1.5 L]. The grade of alumina employed depended on the polarity of the porphyrin (see Supporting Information). The porphyrin-containing fraction was collected and concentrated to afford a purple solid.

5,15-Bis(4-*tert*-butylphenyl)-10,20-bis(4-ethylphenyl)porphinatomagnesium(II) (Mg-1a). Following Method 4A, DBU (3.64 mL, 24.4 mmol, 10.0 mol equiv versus **6a**) was added dropwise to a solution of **6a** (1.00 g, 2.44 mmol, 100 mM) in toluene (24.4 mL). $MgBr_2$ (1.35 g, 7.32 mmol, 3.00 mol equiv) was added. The reaction mixture was heated to reflux (oil bath temperature 135 °C) with exposure to air for the overnight duration of the reaction. TLC analysis (silica, CH_2Cl_2) showed the free base porphyrin, magnesium porphyrin and a trace amount of **6a** (although alumina chromatography was successful, TLC analysis on alumina did not give a successful separation whereas that on silica resulted in better separation). Chromatography [alumina, 500 g, 4 cm dia × 40 cm, CH_2Cl_2/ethyl acetate (4:1 → 3:1)] afforded a trace (0.0040 g, 0.45%) of free base porphyrin (**1a**), which eluted first and was easily isolated apart from the title magnesium porphyrin. The dominant magnesium porphyrin-containing fraction was isolated to give the title compound as a purple solid (0.511 g, 52%): ^{1}H NMR (THF-d_8) δ 1.54 (t, J = 7.6 Hz, 6H), 1.62 (s, 18H), 3.02 (q, J = 7.6 Hz, 4H), 7.56 (d, J = 7.8 Hz, 4H), 7.73 (d, J = 7.8 Hz, 4H), 8.10−8.15 (m, 8H), 8.77 (s, 8H); ^{13}C NMR (THF-d_8) δ 15.4, 28.9, 31.3, 34.7, 121.5, 123.1, 125.6, 131.3, 131.4, 134.9, 135.0, 141.7, 142.0, 142.8, 149.7, 149.8 (the signals of two carbons were not observed); LD-MS obsd 804.8; FAB-MS obsd 804.4073, calcd 804.4042 ($C_{56}H_{52}MgN_4$); λ_{abs} 405, 426, 564, 605 nm.

Condensation of a 1-Acyldipyrromethane via Conventional Heating at 115 °C (Method 4B). The experimental protocol for *trans*-A_2B_2 magnesium porphyrin synthesis was carried out with the oil bath temperature set at 115 °C while keeping the rest of the procedure unchanged.

5,15-Bis(4-methylphenyl)-10,20-di-3-pyridylporphinatomagnesium(II) (Mg-1f). Following Method 4B, **6f** (0.171 g, 0.500 mmol) in toluene (5 mL) was treated with DBU (1.49 mL, 10.0 mmol, 20 mol equiv) and $MgBr_2$ (0.276 g, 1.50 mmol, 3.0 mol equiv). The reaction was complete in 30 min. The crude reaction mixture was allowed to cool and then concentrated. The resulting residue was dissolved in CH_2Cl_2 and filtered through a column [alumina grade V,[93] CH_2Cl_2/triethylamine (100:1)]. The porphyrin-containing fraction was collected and concentrated. The resulting solid was treated with methanol (5 mL), and the resulting suspension was centrifuged. Solvent was decanted, and the remaining purple solid was collected. This procedure (treat with methanol, centrifuge, and decant) was repeated twice to afford a purple solid (72 mg, 43%): LD-MS 666.6, ESI-MS obsd 667.2449, calcd 667.2455 [$(M + H)^+$, M = $C_{44}H_{32}N_4$]; λ_{abs} (hot THF) 408, 429, 571, 614 nm. Due to extensive aggregation upon attempted ^{1}H NMR spectroscopy, a sample of the magnesium porphyrin (42.5 mg, 0.0637 mmol) was demetalated in CH_2Cl_2 (10 mL) by addition of TFA (1.5 mL). The resulting crude reaction mixture was neutralized by the addition of triethylamine (5.0 mL). Aqueous workup and washing with methanol afforded the free base porphyrin **1f** as a purple powder (32.5 mg, 80%): ^{1}H NMR (300 MHz) δ −2.75 (s, 2H), 2.72 (s, 6H), 7.58 (d, J = 7.4 Hz, 4H), 7.73−7.77 (m, 2H), 8.12 (d, J = 7.4 Hz, 4H), 8.52−8.56 (m, 2H), 8.82 (d, J = 4.8 Hz, 4H), 8.97 (d, J = 4.8 Hz, 4H), 9.06−9.08 (m, 2H), 9.50−9.51 (m, 2H); ^{13}C NMR (75 MHz) δ 21.7, 116.1, 121.2, 122.2, 127.7, 130.0−131.5 (brs), 131.8−132.8 (brs), 134.7, 137.8, 138.3, 139.0, 141.1, 149.3, 153.9; LD-MS 644.3, ESI-MS obsd 645.2765 calcd 645.2761 [$(M + H)^+$, M = $C_{44}H_{32}N_4$]; λ_{abs} 421, 517, 550, 592, 651 nm.

Condensation of a 1-Acyldipyrromethane via Microwave Irradiation (Method 5, as used in Table 2). A sample of 1-acyldipyrromethane (0.10 mmol) was placed in a 10 mL glass tubular reaction vessel containing a magnetic stir bar. Toluene (1.0 mL) and DBU (0.150 mL, 1.00 mmol) were added. The resulting mixture was stirred to obtain a homogeneous solution and then treated with $MgBr_2$ (0.055 g, 0.30 mmol). The vessel was sealed with a septum and subjected to microwave irradiation at 100 W. The protocol was as follows: (1) heat from room temperature to 115 °C (irradiate for 2 min), (2) hold at 115 °C (irradiate for 15 min; temperature typically overshot to 135 °C and then stabilized after 2 min), (3) allow to cool to room temperature (∼1 min), (4) check the reaction mixture by TLC analysis and absorption spectroscopy, (5) repeat steps 1−3 until porphyrin formation is complete. The reaction mixture was transferred to a round-bottom flask (using THF, which was HPLC grade and lacked stabilizer) and concentrated. The resulting crude product was filtered through a column [alumina grade V,[93] CH_2Cl_2 → CH_2Cl_2/ethyl acetate (1:1) → ethyl acetate → THF/MeOH (10:1)]. The porphyrin-containing fractions were concentrated. The resulting porphyrin was suspended in hexanes (5 mL). The suspension was sonicated for ∼1 min, centrifuged, and decanted to obtain the powder. The resulting porphyrin was suspended in methanol (5 mL) and treated likewise (sonication, centrifugation, decantation) to afford a purple powder.

5,15-Di-3-pyridyl-10,20-di-4-pyridylporphinatomagnesium(II) (Mg-1o). Following Method 5, a sample of **6o** (0.0330 g, 0.100 mmol) gave porphyrin in 45 min. Chromatography [CH_2Cl_2 → CH_2Cl_2/ethyl acetate (1:1) → ethyl acetate → THF/MeOH (20:1)] followed by washing the porphyrin suspension with hexanes and methanol afforded a purple powder (14 mg, 21%): ^{1}H NMR

(86) Shi, B. L.; Boyle, R. W. *J. Chem. Soc. Perkin Trans. 1* **2002**, 1397–1400.
(87) Suzuki, M.; Osuka, A. *Org. Lett.* **2003**, *5*, 3943–3946.
(88) Manka, J. S.; Lawrence, D. S. *Tetrahedron Lett.* **1989**, *30*, 6989–6992.
(89) Leanord, D. R.; Smith, J. R. L. *J. Chem. Soc. Perkin Trans. 2* **1990**, 1917–1923.
(90) (a) Little, R. G. *J. Heterocyclic Chem.* **1981**, *18*, 833–834. (b) Little, R. G.; Anton, J. A.; Loach, P. A.; Ibers, J. A. *J. Heterocyclic Chem.* **1975**, *12*, 343–349.
(91) Fleischer, E. B. *Inorg. Chem.* **1962**, *1*, 493–495.
(92) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827–836.
(93) Li, F.; Gentemann, S.; Kalsbeck, W. A.; Seth, J.; Lindsey, J. S.; Holten, D.; Bocian, D. F. *J. Mater. Chem.* **1997**, *7*, 1245–1262.

(DMSO-d_6) δ 7.03−7.07 (m, 2H), 7.38−7.39 (br, 4H), 7.76−7.78 (m, 2H), 7.93 (d, J = 6.2 Hz, 4H), 7.98 (d, J = 6.2 Hz, 4H), 8.17−8.19 (m, 6H), 8.46−8.54 (br, 2H); LD-MS obsd 640.6, ESI-MS obsd 641.2044, calcd 641.2047 [(M + H)$^+$, M = $C_{40}H_{24}MgN_8$]; λ_{abs} (toluene) 407, 428, 564, 604 nm.

Statistical Condensation of Two 1-Acyldipyrromethanes via Microwave Irradiation (Method 6). Samples of a first 1-acyldipyrromethane (0.20 mmol) and a second 1-acyldipyrromethane (0.20 mmol) were placed in a 10 mL glass tubular reaction vessel containing a magnetic stir bar. Toluene (4.0 mL) and DBU (0.60 mL, 4.0 mmol) were added. The resulting mixture was stirred to obtain a homogeneous solution and then treated with $MgBr_2$ (0.221 g, 1.20 mmol). The vessel was sealed with a septum and subjected to microwave irradiation at 100 W. The protocol was as follows: (1) heat from room temperature to 115 °C (irradiate for 2 min), (2) hold at 115 °C (irradiate for 15 min; temperature typically overshot to 135 °C and then stabilized after 2 min), (3) allow to cool to room temperature (∼1 min), (4) check the reaction mixture by TLC analysis and absorption spectroscopy, and (5) repeat steps 1−3 until porphyrin formation is complete. After porphyrin formation was complete, the crude reaction mixture was transferred to a round-bottom flask (using THF, which was HPLC grade and lacked stabilizer) and concentrated. The resulting crude product was washed (water, brine), dried (Na_2SO_4), and concentrated. The resulting crude reaction mixture was dissolved in CH_2Cl_2 (4 mL) and demetalated by the addition of TFA (0.032 mL). A sample of triethylamine was added (0.020 mL). The crude reaction mixture was washed (water, brine), dried (Na_2SO_4), and concentrated. The resulting product was chromatographed [silica, CH_2Cl_2 → CH_2Cl_2/ethyl acetate (1:3) → ethyl acetate → ethyl acetate/MeOH (10:1)]. Each porphyrin-containing fraction was concentrated. The resulting porphyrin was suspended in hexanes (5 mL). The suspension was sonicated for ∼1 min, centrifuged, and decanted to obtain the powder. The resulting porphyrin was suspended in methanol (5 mL) and treated likewise (sonication, centrifugation, decantation) to afford a purple powder.

Note that when one of the 1-acyldipyrromethanes was 1-formyldipyrromethane (**6z**), the order of elution typically was porphine, the target "hybrid" porphyrin, and the porphyrin derived from condensation of two molecules of the other 1-acyldipyrromethane. When one of the 1-acyldipyrromethanes was 1-hexanoyl-5-pentyldipyrromethane (**6r**), the order of elution typically was the target "hybrid"porphyrin followed by the porphyrin derived from condensation of two molecules of the other 1-acyldipyrromethane; no tetrapentylporphyrin was obtained.

5,10-Di-3-pyridylporphyrin (2b). Following Method 6, a mixture of **6l** (0.066 g, 0.20 mmol) and **6z** (0.035 g, 0.20 mmol) in toluene (4 mL) was treated with DBU (0.60 mL, 4.0 mmol) and $MgBr_2$ (0.220 g, 1.20 mmol). Chromatography followed by washing the porphyrin with hexanes (5 mL) and methanol (5 mL) afforded the title compound as a purple powder (0.026 g, 28%): ^{1}H NMR δ −3.47 (s, 2H), 7.73−7.78 (m, 2H), 8.50−8.52 (m, 2H), 8.90 (s, 2H), 8.96 (d, J = 6.6 Hz, 2H), 9.06−9.08 (m, 2H), 9.38 (d, J = 6.6 Hz, 2H), 9.41−9.43 (brs, 2H), 9.44−9.47 (brs, 2H), 10.24 (s, 2H); ^{13}C NMR δ 105.2, 115.9, 122.2, 131.1−132.9 (brs), 138.1, 141.2, 149.4, 153.9; LD-MS obsd 464.4; ESI-MS obsd 465.1819, calcd 465.1822 [(M + H)$^+$, M = $C_{30}H_{20}N_6$]; λ_{abs} (toluene) 409, 502, 534, 577 nm. Two other porphyrins also were isolated, 5,10,15,20-tetra-3-pyridylporphyrin (**1l**, 4 mg, 3%) and porphine (0.0080 g, 26%). Data for **1l**: ^{1}H NMR (300 MHz) δ −2.84 (s, 2H), 7.68−7.72 (m, 4H), 8.05−8.11 (m, 4H), 8.19−8.21 (m, 4H), 8.84−8.8 (brs, 8H), 9.12−9.14 (brs, 4H); ^{13}C NMR δ 117.0, 122.3, 131.2−131.8 (brs), 137.8, 141.2, 149.6, 153.9, 160.8; ESI-MS obsd 619.2355, calcd 619.2353 [(M + H)$^+$, M = $C_{40}H_{26}N_8$]; λ_{abs} (toluene) 420, 515, 550, 592, 648 nm. The data (^{1}H NMR, ^{13}C NMR, FAB-MS) for porphine were consistent with those obtained from an authentic sample.[8]

5-(4-Pyridyl)porphyrin (2h). Following Method 6, a mixture of **6w** (0.050 g, 0.20 mmol) and **6z** (0.035 g, 0.20 mmol) in toluene (4 mL) was treated with DBU (0.60 mL, 4.0 mmol) and $MgBr_2$ (0.220 g, 1.20 mmol). Chromatography [silica, THF → THF/MeOH (10:1)] followed by washing the porphyrin with hexanes (5 mL) afforded the title compound as a purple powder (0.016 g, 21%): ^{1}H NMR δ −3.69 (s, 2H), 8.17−8.19 (m, 2H), 9.02−9.06 (m, 4H), 9.43−9.44 (m, 2H), 9.42−9.48 (m, 4H), 10.28 (s, 1H), 10.34 (m, 2H); ^{13}C NMR δ 104.5, 105.2, 115.9, 129.9, 130.1, 130.7, 131.7, 132.2, 148.6, 150.2; ESI-MS obsd 388.1554, calcd 388.1556 [(M + H)$^+$, M = $C_{25}H_{17}N_5$]; λ_{abs} (toluene) 402, 495, 527, 569 nm. Two other porphyrins also were isolated, 5,15-di-4-pyridylporphyrin (**1w**, 0.010 g, 11%) and porphine (trace). No ESI-MS signal was observed for **1w** because of low solubility.

5,10-Dipentyl-15,20-di-4-pyridylporphyrin (3c). Following Method 6, a mixture of **6m** (0.033 g, 0.10 mmol) and **6r** (0.031 g, 0.10 mmol) in toluene (2 mL) was treated with DBU (0.30 mL, 2.0 mmol) and $MgBr_2$ (0.110 g, 0.600 mmol). The reaction was monitored with TLC analysis [silica, THF/MeOH (10:1)] and absorption spectroscopy. Porphyrin formation was complete in ∼2 h. TLC analysis of the crude reaction mixture [silica, CH_2Cl_2 → CH_2Cl_2/ethyl acetate (1:1) → THF/MeOH (10:1)] revealed two green spots (R_f = 0.32 and 0.61). The absorption spectrum of the crude reaction mixture revealed four bands (303, 405, 425, and 564 nm). The LD-MS analysis (with POPOP) of the crude reaction mixture indicated the presence of two porphyrins. The molecule ion peak, m/z = 626.9, was assigned to **Mg-3c**, whereas the peak at m/z = 640.6 was consistent with porphyrin **Mg-1m**. The crude product was dissolved in CH_2Cl_2 and demetalated by addition of TFA. The reaction mixture was neutralized with triethylamine. Aqueous workup and chromatography [silica, CH_2Cl_2 → CH_2Cl_2/ethyl acetate (1:1) → ethyl acetate/MeOH (10:1)] afforded the title compound as a purple powder (0.016 g, 26%): ^{1}H NMR δ −2.77 (s, 2H), 0.97 (t, J = 7.2 Hz, 6H), 1.54−1.57 (m, 4H), 1.75−1.83 (m, 4H), 2.50−2.58 (m, 4H), 4.98−5.01 (m, 4H), 8.10 (d, J = 5.8 Hz, 4H), 8.67−8.72 (brs, 2H), 8.79 (d, J = 4.4 Hz, 2H), 9.00 (d, J = 5.8 Hz, 4H), 9.48 (d, J = 4.4 Hz, 2H), 9.57−9.61 (brs, 2H); LD-MS obsd 604.7, ESI-MS obsd 605.3382, calcd 605.3387 [(M + H)$^+$, M = $C_{40}H_{40}N_6$]; λ_{abs} (toluene) 419, 517, 551, 595, 652 nm. 5,10,15,20-Tetra-4-pyridylporphyrin (**1m**) also was isolated (0.0076 g, 12%): ^{1}H NMR δ −2.93 (s, 2H), 8.15−8.17 (m, 8H), 8.85−8.88 (brs, 8H), 9.06−9.08 (m, 8H); ESI-MS obsd 619.2371, calcd 619.2353 [(M + H)$^+$, M = $C_{40}H_{26}N_4$]; λ_{abs} (THF) 408, 429, 529, 569, 611 nm.

Quaternization Procedure to Yield 5,10-Dipentyl-15,20-bis[4-methylpyridin-4-ium-1-yl]porphyrin Diiodide (3c-Me$_2$I$_2$). A solution of **3c** (0.020 g, 0.033 mmol) in chloroform (3.3 mL) was treated with excess iodomethane (0.410 mL, 6.62 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated, and the resulting product was washed with hexanes (5 mL × 2) to afford the title compound as a purple powder (0.0264 g, 90%): ^{1}H NMR (DMSO-d_6) δ −2.88 (s, 2H), 0.93 (t, J = 7.4, 6H), 1.46−1.54 (m, 4H), 1.73−1.78 (m, 4H), 2.53−2.55 (overlapped with DMSO signal), 4.70 (s, 6H), 4.98−5.11 (m, 4H), 8.94−8.96 (m, 8H), 9.43−9.45 (m, 4H), 9.14−8.16 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 14.7, 23.0, 32.6, 48.5, 113.0, 124.2, 132.9, 144.7, 157.9 (not all carbon signals were observed owing to limited solubility); ESI-MS obsd 317.1893, calcd 317.1886 [(M − 2I)$^{2+}$, M = $C_{42}H_{46}I_2N_6$]; λ_{abs} (water) 419, 525, 563, 646 nm.

Yield Calculations for Statistical Reactions (Tables 3 and 4). The yield of porphyrin formation via condensation of equal quantities of two nonidentical 1-acyldipyrromethanes (e.g., 0.10 mmol each) was calculated as follows: (1) the theoretical yield of porphyrins in total was equal to one-half the sum total number of millimoles of dipyrromethane species, (2) the actual yield in mmol of each porphyrin was determined experimentally, and (3) the ratio of the actual yield to the theoretical yield in total gives the reported % yield for each component. In this manner, the sum of all % yields can equal but not exceed 100%. Also, if each of the two 1-acyldipyrromethanes exclusively underwent homocondensation to give the two porphyrins derived therefrom with no heterocon-

densation to give hybrid porphyrin, the yield of each would be 50%, again giving a total of 100%. Conversely, if exclusive heterocondensation occurred, the yield of hybrid porphyrin would be 100%.

Acknowledgment. This research was supported by the NIH (GM36238). Mass spectra were obtained at the Mass Spectrometry Laboratory for Biotechnology at North Carolina State University. Partial funding for the Facility was obtained from the North Carolina Biotechnology Center and the National Science Foundation.

Supporting Information Available: Survey of reaction conditions; procedures for preparing compounds; experimental section; and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800588N