Organic Process Research & Development **2005**, *9*, 651−659

Refined Synthesis of 2,3,4,5-Tetrahydro-1,3,3-trimethyldipyrrin, a Deceptively Simple Precursor to Hydroporphyrins

Marcin Ptaszek, Jayeeta Bhaumik, Han-Je Kim, Masahiko Taniguchi, and Jonathan S. Lindsey*

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

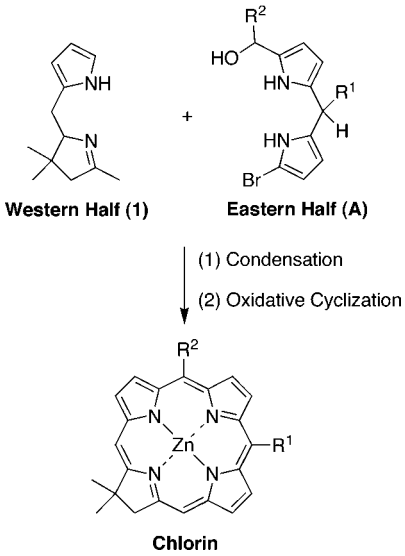
Abstract:

2,3,4,5-Tetrahydro-1,3,3-trimethyldipyrrin (1) is a crucial building block in the rational synthesis of chlorins and oxochlorins. The prior five-step synthesis of 1 from pyrrole-2-carboxaldehyde (2) employed relatively simple and well-known reactions yet suffered from several drawbacks, including limited scale (≤0.5 g of 1 per run). A streamlined preparation of 1 has been developed that entails four steps: (i) nitro-aldol condensation of 2 and nitromethane under neat conditions to give 2-(2-nitrovinyl)pyrrole (3), (ii) reduction of 3 with $NaBH_4$ to give 2-(2-nitroethyl)pyrrole (4), (iii) Michael addition of 4 with mesityl oxide under neat conditions or at high concentration to give γ-nitrohexanone-pyrrole 5, and (iv) reductive cyclization of 5 with zinc/ammonium formate to give 1. Several multistep transformations have been established, including the direct conversion of 2 → 1. The advantages of the new procedures include (1) fewer steps, (2) avoidance of several problematic reagents, (3) diminished consumption of solvents and reagents, (4) lessened reliance on chromatography, and (5) scalability. The new procedures facilitate the preparation of 1 at the multigram scale.

Introduction

Hydroporphyrins (e.g., chlorins, bacteriochlorins, isobacteriochlorins) are naturally occurring pigments with diverse functions. Methods for preparing chlorins have been aimed at total syntheses of naturally occurring compounds as well as more simple syntheses of chlorins for use in a variety of applications.[1] We recently developed rational syntheses of non-natural chlorins[2−4] (Scheme 1) and oxochlorins[5] by extending routes developed by Battersby for the synthesis of naturally occurring hydroporphyrins.[6] The synthesis entails reaction of an Eastern half (**A**) with a Western half (**1**) to form a tetrahydrobilene-*a*, which upon oxidative cyclization affords the zinc chlorin. The Eastern half is easily available.[2,4,7] However, the synthesis of the Western half has presented a number of challenges.

Scheme 1



Our previous route to **1**, which entailed five steps, is summarized in Scheme 2. The synthesis involved (i) nitro-aldol condensation of pyrrole-2-carboxaldehyde (**2**) with nitromethane,[2] (ii) $NaBH_4$ reduction of nitrovinylpyrrole **3**,[2] (iii) Michael addition of nitroethylpyrrole **4** to mesityl oxide,[2] (iv) reductive cyclization of nitrohexanone **5** by Zn/AcOH,[4] and (v) deoxygenation of *N*-oxide **6** using Ti(0) prepared in situ.[2]

Compound **1** appears quite simple, but the appearance is deceptive because the two different heterocycles (pyrrole, pyrroline) present quite distinct reactivity. The complexity of the chemistry presented by **1** is as follows: (1) the pyrrole contains three open sites for electrophilic substitution, (2) the pyrrole is activated toward electrophiles by the 2-alkyl substituent, (3) the imine is susceptible to reduction and addition, (4) the imine nitrogen can coordinate to metals, (5) the pyrrole is a weak acid whereas the pyrroline is a weak base, and (6) the α-pyrrolic methylene is susceptible to oxidation. In addition, tetrahydrodipyrrin **1** undergoes intramolecular cyclization in the presence of acid, forming a pyrrolo[3.2.1]azabicyclooctane byproduct (**7**) (eq 1).[4] Precursors **2**−**6** also are sensitive to a number of reaction conditions. Thus, the scope of suitable synthetic methods is limited.

* Corresponding author. E-mail: jlindsey@ncsu.edu.

(1) (a) Montforts, F.-P.; Gerlach, B.; Höper, F. *Chem. Rev.* **1994**, *94*, 327−347. (b) Chen, Y.; Li, G.; Pandey, R. K. *Curr. Org. Chem.* **2004**, *8*, 1105−1134.

(2) Strachan, J.-P.; O'Shea, D. F.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 3160−3172.

(3) Balasubramanian, T.; Strachan, J. P.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7919−7929.

(4) Taniguchi, M.; Ra, D.; Mo, G.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2001**, *66*, 7342−7354.

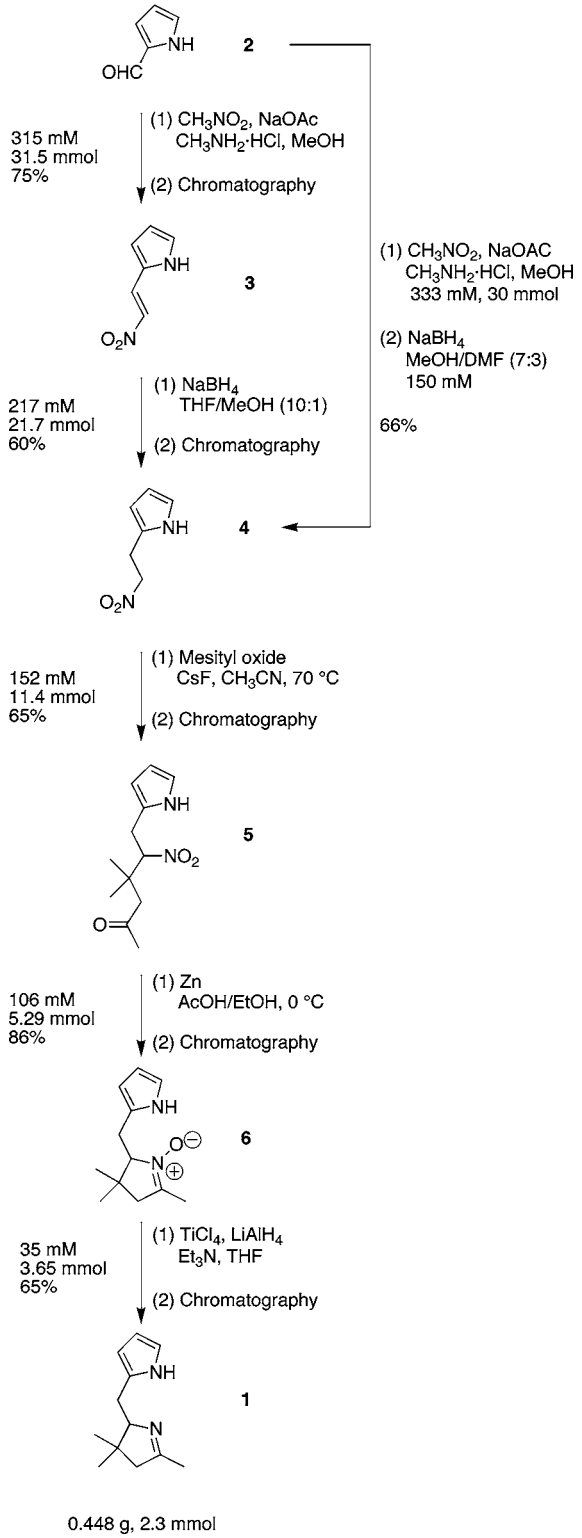
(5) Taniguchi, M.; Kim, H.-J.; Ra, D.; Schwartz, J. K.; Kirmaier, C.; Hindin, E.; Diers, J. R.; Prathapan, S.; Bocian, D. F.; Holten, D.; Lindsey, J. S. *J. Org. Chem.* **2002**, *67*, 7329−7342.

(6) Battersby, A. R.; Fookes, C. J. R.; Snow, R. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2725−2732.

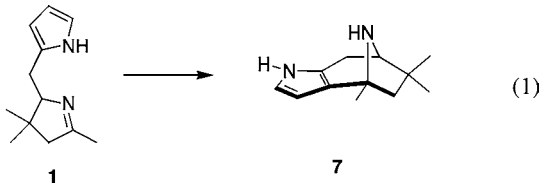
(7) (a) Rao, P. D.; Littler, B. J.; Geier, G. R., III; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 1084−1092. (b) Muthukumaran, K.; Ptaszek, M.; Noll, B.; Scheidt, W. R.; Lindsey, J. S. *J. Org. Chem*. **2004**, *69*, 5354−5364.

10.1021/op050087e CCC: $30.25
Published on Web 08/10/2005

Scheme 2

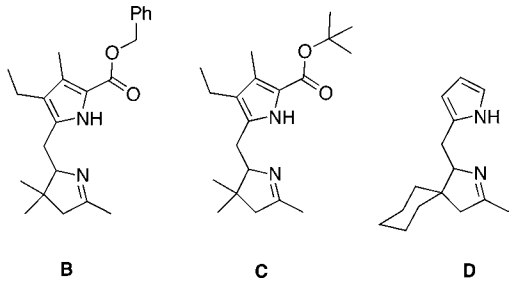


One of the significant structural differences between **1** and tetrahydrodipyrrinic analogues reported earlier by Battersby (Chart 1, compounds **B** and **C**)[6] is that the latter have two β-substituents in the pyrrolic ring, whereas **1** and derivatives thereof (**D**)[5] typically have no pyrrolic β-substituents. In general, tetrahydrodipyrrins lacking β-pyrrolic substituents have been prepared in lower overall yield and have required milder reaction conditions than the more stable β-substituted species. Indeed, treatment of **C** in neat TFA at



(1)

Chart 1



room temperature yields the decarboxylated tetrahydrodipyrrin, which is stable to the strong acid,[6] whereas **1** undergoes slow cyclization in the presence of dilute TFA to afford the byproduct **7**[4] (eq 1). In addition, the byproduct **7** was observed upon reductive cyclization of nitrohexanone **5** in AcOH and was the main product upon attempted deoxygenation of **5** using Ti(III) at pH 6.[4] Thus, deoxygenation methods developed for β-substituted pyrrolic derivatives provided a low yield of **1**. Regardless, each tetrahydrodipyrrin was prepared at relatively small scale (448 mg of **1**,[4] 139 mg of **B**,[6] 914 mg of **C**,[6] 228 mg of **D**[5]). Attempts to increase the scale of synthesis of **1** met with several obstacles. First, each intermediate was purified by chromatography. Some synthetic steps required low concentrations and a large excess of reagents, hence increasing the scale was prohibitive in terms of solvent and materials consumption. Moreover, the yields of most of the synthetic steps decreased substantially upon increasing the scale, which we attributed to the instability of the various reactants under the conditions employed.

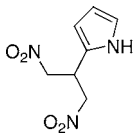
In this paper we report a refined preparation of **1** that proceeds in reasonable yield, with limited chromatography, and diminished consumption of solvents and reactants. The number of steps in the synthesis has been reduced from five to four, two or one. Taken together, the improvements have enabled the routine preparation of **1** at 60-mmol scale to afford 2.5 g of product in shorter time (3 days) or at medium scale (0.4 mol) to give 11 g of **1** (22 times more than reported previously). Application of this methodology to substituted analogues of **1** will be described elsewhere.

Results and Discussion

I. Refinement of Individual Transformations. A. Nitroaldol Condensation (2 → 3). The typical conditions for the nitro-aldol condensation of pyrrole-2-carboxaldehyde require the presence of an ammonium salt and/or weak base. The condensation of pyrrole-2-carboxaldehyde with a nitroalkane typically is done in the presence of one of the following:

ammonium acetate,[8] ammonium acetate with microwave irradiation,[9] ethylenediamine,[10] sodium acetate,[11] or a mixture of methylamine hydrochloride and sodium acetate.[2−6] The latter reagent affords superior results for *N*-unprotected pyrrole-2-carboxaldehydes, whereas the former reagents are more suitable for *N*-substituted pyrrolic derivatives. However, methylamine hydrochloride is scrutinized by U.S. drug enforcement agencies owing to use in methamphetamine syntheses; hence, we searched for a comparable reagent for the first step of the synthesis. The amine must be easily removed from the reaction mixture (to proceed to the next step without laborious workup) and enable reaction at high concentration or even under solventless conditions (to diminish the use of solvents in large-scale preparations).

Various catalytic systems for the nitro-aldol condensation were examined to identify conditions that meet three objectives: (1) complete consumption of **2**, (2) good yield of product **3**, and (3) little or no black byproducts. The results of a survey of different amines and ammonium salts and the influence of a water scavenger (molecular sieves) are listed in the Supporting Information. The cleanest reaction and the mildest condition were obtained with **2** dissolved in a 3-fold excess of nitromethane (no other solvent) containing AcOH/*n*-$PrNH_2$ (0.60 equiv/0.55 equiv) at room temperature (Scheme 3). The reaction is complete within 2−3 h. The ratio of AcOH/*n*-$PrNH_2$ is critical. A slight excess of *n*-propylamine caused formation of a significant amount of dark byproducts, which interfered with the workup and resulted in a lower yield. On the other hand, a slight excess (0.57−0.60 equiv) of acetic acid provided a relatively clean product with minor amounts of dark byproducts. The small excess of acid also diminished the Michael addition of nitromethane to the 2-(2-nitrovinyl)pyrrole (**3**), which forms the ostensible byproduct 2-(2-pyrrolyl)-1,3-dinitropropane (**8**). An analogous byproduct was observed upon similar

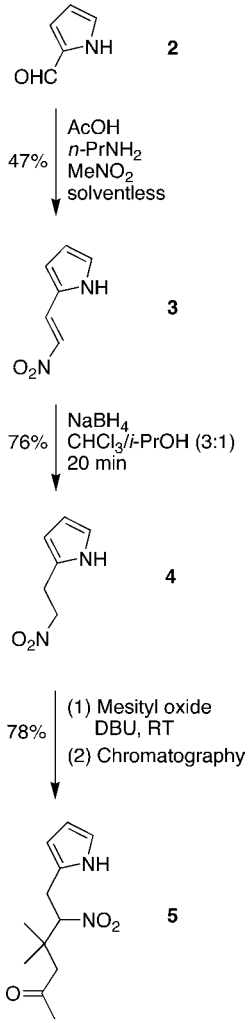


8

reaction of a 3-(4-iodophenyl)-2-(2-nitrovinyl)pyrrole.[3] A small amount of **8**, which was detected in the crude reaction mixture, can be easily separated by precipitation of **3** from CH_2Cl_2/hexanes. Another problem encountered was an exothermic reaction between AcOH and *n*-$PrNH_2$. Therefore, the salt was prepared in a small amount of methanol in a separate flask and then transferred to the solution of pyrrole-2-carboxaldehyde.

Another issue was the choice of workup procedure suitable for the next step. 2-(2-Nitrovinyl)pyrrole (**3**) is

Scheme 3



somewhat unstable; therefore for this reason alone, chromatography should be avoided. Treatment of the crude reaction mixture with $NaBH_4$ (in an appropriate solvent) did not prove fruitful, as 2-(2-nitroethyl)pyrrole (**4**) was obtained in low yield accompanied by several byproducts. An effective workup was achieved by washing the crude mixture containing **3** with water and then removing excess $MeNO_2$ under high vacuum.

B. Reduction of 2-(2-Nitrovinyl)pyrrole (3 → 4). The previous synthetic route utilized $NaBH_4$ in DMF/THF or MeOH/THF.[2,4] This procedure required a large excess of $NaBH_4$ (3.5 mol equiv) and gave a nonreproducible yield at larger scale owing to the formation of byproducts. Moreover, the abundant boron salts caused difficulties in purification of the final product. Use of a different solvent system ($CHCl_3$/2-propanol, 3:1) in the presence of silica[12] enabled use of a lesser quantity of $NaBH_4$ (2 mol equiv), diminished the amount of byproducts, and gave the desired product in 76% yield (Scheme 3). Additionally, the presence of silica in the reaction mixture facilitated purification. Most of the impurities were absorbed on the silica, and filtration through a pad of silica afforded the pure **4**.

C. Michael Addition with Mesityl Oxide (4 → 5). The previously reported procedures for Michael addition of

(8) (a) Hamdan, A.; Wasley, J. W. F. *Synth. Commun.* **1985**, *15*, 71−74. (b) Dumoulin, H.; Rault, S.; Robba, M. *J. Heterocycl. Chem.* **1997**, *34*, 13−16. (c) Fuji, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1992**, *40*, 2344−2352.

(9) Kuster, G. J. T.; Steeghs, R. H. J.; Scheeren, H. W. *Eur. J. Org. Chem.* **2001**, 553−560.

(10) Aleksiev, D. I.; Ivanova, S. M. *Russ. J. Org. Chem.* **1993**, *29*, 1845−1847.

(11) Khorana, N.; Smith, C.; Herrick-Davis, K.; Purohit, A.; Teitler, M.; Grella, B.; Dukat, M.; Glennon, R. A. *J. Med. Chem.* **2003**, *46*, 3930−3937.

(12) Sinhababu, A. K.; Borchardt, R. T. *Tetrahedron Lett.* **1983**, *24*, 227−230.

Table 1. **Conditions for the Michael addition (4 → 5)[a]**

entry	base (equiv)	**4**: equiv, solvent (concentrated)	temp (°C)	time (h)	yield of **5**[b]
1[c]	CsF (5.7)	5.0, CH_3CN (150 mM)[d]	70	16	65%[e]
2	CsF (3.0)	10, CH_3CN (350 mM)[f]	80	18	61%[e]
3	CsF (3.0)	10, neat	60	14	none[g]
4	CsF (3.0)	10, neat	rt	18	trace[g]
5	Al_2O_3	1.0, neat	rt	14	none
6	DBU (1.0)	2.0, CH_3CN (200 mM)	reflux	4	50%
7	DBU (1.0)	1.1, THF (500 mM)	rt	3	trace
8	DBU (1.0)	1.1, THF (500 mM)	reflux	1	trace
9	DBU (1.0)	10, neat	rt	14	75%
10	DBU (3.0)	10, neat	rt	16	78%[e]
11	TMG (0.25)	1.1, THF (250 mM)	rt	14	none
12	TMG (1.25)	1.1, THF (250 mM)	rt	1	trace
13	TMG (0.25)	1.1, CH_3CN (250 mM)	rt	14	trace

[a] The reactions were carried out with 1 mmol of **4** unless noted otherwise. [b] Yields were estimated on the basis of GC. [c] Conditions employed previously.[2] [d] 11.4 mmol scale. [e] Isolated yield. [f] 25 mmol scale. [g] Extensive byproducts.

mesityl oxide and 2-(2-nitroethyl)pyrroles utilized fluoride anion (e.g., TBAF[13] or CsF[2−5]) to effect reaction (entry 1, Table 1). We examined CsF and other reagents in the reaction of **4** with excess mesityl oxide (10 equiv) that have been reported to be effective for the Michael addition of α,β-enones and nitroalkanes (Al_2O_3,[14] DBU,[15] and TMG[16]). The ideal reagent should give a clean reaction, a good yield at high concentration (or even neat conditions), and be easily removed from the reaction mixture. The reaction with CsF in refluxing CH_3CN gave 61% yield (entry 2), but reaction under neat conditions either at 60 °C (entry 3) or room temperature (entry 4) gave no product. Reaction with alumina under neat conditions also gave no product (entry 5). Replacement of CsF with DBU in refluxing CH_3CN gave 50% yield (entry 6). Replacing CH_3CN with THF gave only a trace of product (entries 7 and 8). On the other hand, the reaction with DBU under neat conditions at room temperature gave **5** in high yield (entries 9 and 10). Attempts to use tetramethylguanidine (TMG) in place of DBU gave little or no product (entries 11−13).

The advantages of DBU versus CsF include slightly higher yield, lower cost, absence of solvent, and greater ease of handling (no requirement for desiccation). The results shown in Table 1 employ 10 equiv of mesityl oxide and were performed using 1 mmol of **4**. Although mesityl oxide is inexpensive, an excess is unattractive for applications envisaged with more valuable enones. We found that the Michael addition also proceeded well with lesser quantities of mesityl oxide as long as the reaction time was prolonged. Thus, application of the best conditions (DBU, solventless, room temperature; entry 10) with 10.0 mmol of **4** but only 1.1 equiv of mesityl oxide for 24 h afforded **5** in 78% yield.

D. Reductive Cyclization (5 → 1). The previous reduction of nitrohexanone **5** to the tetrahydrodipyrrin **1** was performed in two-steps: cyclization to the *N*-oxide **6** followed by deoxygenation of **6**. This procedure suffers from several problems: (1) the yield of both steps decreased substantially with increasing scale, (2) both steps required a large excess of metal reagents (25 equiv of zinc, 7 equiv of $TiCl_4$), and (3) the deoxygenation step was done at relatively low concentration (35 mM). To scale-up the synthesis of **1** necessitated a significant improvement in each step.

Several mild methods are known for direct reductive cyclization of γ-nitro-ketones to the corresponding cyclic imines,[16] reduction of nitroalkanes to the corresponding amines,[17] or the deoxygenation of *N*-oxides.[18] Some recent pertinent examples include the following:

(a) γ-nitro-ketones → cyclic imines: Zn/NH_4Cl,[16a] Fe/NH_4Cl,[16b] $NiCl_2 \cdot H_2O$/$NaBH_4$/$NH_2NH_2 \cdot H_2O$,[16c] Pd−C/$HCOONH_4$,[16d] and Zn/HCOOH;[16e]

(b) nitroalkanes → amines: $NH_2NH_2 \cdot H_2O$/graphite,[17a] $NH_2NH_2 \cdot H_2O$/Raney Ni,[17b] Zn/$HCOONH_4$,[17c] Mg/$HCOONH_4$,[17d] Mg/NH_2NH_2,[17e] Zn/NH_2NH_2/HCOOH,[17f] and $ZrCl_4$/$NaBH_4$;[17g]

(c) deoxygenation of *N*-oxides: Pd−C/$HCOONH_4$,[18a] Zn/$HCOONH_4$,[18b] In/NH_4Cl,[18c] $InCl_3$,[18d] Ga/H_2O,[18e] and formic pivalic anhydride.[18f] Earlier methods have been reviewed.[18g]

A survey of reducing agents and conditions was carried out for the direct conversion of the γ-nitro-ketone **5** to the tetrahydrodipyrrin **1** (Scheme 4). Generally, we searched for mild conditions with an aim toward application at >10-g scale. Selected results are shown in Table 2 (for a broader survey, see the Supporting Information). The use of Zn/$HCOONH_4$ gave preferentially the desired target **1** accompanied by limited amounts of *N*-oxide **6** (entries 1−9). The choice of solvent was critical. Although methanol appeared to provide a good conversion of **5** to **1**, the isolated yield was very low (∼10%). We reasoned that the low yield might stem from the formation of a complex between zinc(II) and **1**, as zinc(II) is known to coordinate with the related dipyrrin species forming bis(dipyrrinato)zinc(II) complexes.[19] Accordingly, THF was used, and the isolated yield increased to 60%. The reaction was clean, proceeding at relatively high concentration, and workup was straightforward. Large-scale

(13) Harrison, P. J.; Sheng, Z.-C.; Fookes, C. J. R.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1667−1678.

(14) Ranu, B. C.; Bhar, S.; Sarkar, D. C. *Tetrahedron Lett.* **1991**, *32*, 2811−2812.

(15) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933−971 and references therein.

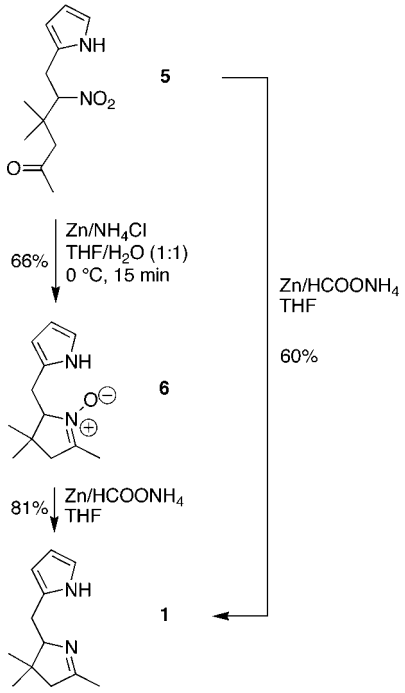
(16) (a) Black, D. S.; Edwards, G. L.; Evans, R. H.; Keller, P. A.; Laaman, S. M. *Tetrahedron* **2000**, *56*, 1889−1897. (b) Take, K.; Okumara, K.; Tsubaki, K.; Terai, T.; Shiokawa, Y. *Chem. Pharm. Bull.* **1993**, *41*, 507−515. (c) Urrutia, A.; Rodriguez, J. G. *Tetrahedron* **1999**, *55*, 11095−11108. (d) Benchekroun-Mounir, N.; Dugat, D.; Gramain, J.-C.; Husson, H.-P. *J. Org. Chem.* **1993**, *58*, 6457−6465. (e) Cheruku, S. R.; Padmanilayam, M. P.; Vennerstrom, J. L. *Tetrahedron Lett.* **2003**, *44*, 3701−3703.

(17) (a) Han, B. H.; Shin, D. H.; Cho, S. Y. *Tetrahedron Lett.* **1985**, *26*, 6233−6234. (b) Gowda, S.; Gowda, D. C. *Tetrahedron* **2002**, *58*, 2211−2213. (c) Gowda, D. C.; Mahesh, B.; Gowda, S. *Ind. J. Chem.* **2001**, *40B*, 75−77. (d) Srinivasa, G. R.; Abiraj, K.; Gowda, D. C. *Ind. J. Chem.* **2003**, *42B*, 2882−2884. (e) Srinivasa, G. R.; Abiraj, K.; Gowda, D. C. *Ind. J. Chem. Sec.* **2003**, *42B*, 2885−2887. (f) Gowda, S.; Gowda, B. K. K.; Gowda, D. C. *Synth. Commun.* **2003**, *33*, 281−289. (g) Chary, K. P.; Ram, S. R.; Iyengar, D. S. *Synlett* **2000**, 683−685.

(18) (a) Balicki, R. *Synthesis* **1989**, 645−646. (b) Balicki, R.; Cybulski, M.; Maciejewski, G. *Synth. Commun.* **2003**, *33*, 4137−4141. (c) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. M. *Tetrahedron Lett.* **2000**, *41*, 2663−2665. (d) Ilias, M.; Barman, D. C.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **2002**, *43*, 1877−1879. (e) Han, J. H.; Choi, K. I.; Kim, J. H.; Yoo, B. W. *Synth. Commun.* **2004**, *34*, 3197−3201. (f) Rosenau, T.; Potthast, A.; Ebner, G.; Kosma, P. *Synlett* **1999**, 623−625. (g) Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, 1991; pp 120−134.

(19) Yu, L.; Muthukumaran, K.; Sazanovich, I. V.; Kirmaier, C.; Hindin, E.; Diers, J. R.; Boyle, P. D.; Bocian, D. F.; Holten, D.; Lindsey, J. S. *Inorg. Chem.* **2003**, *42*, 6629−6647.

Scheme 4



applications appear viable because the yield remains high upon increasing the scale (up to 0.4 mol), inexpensive off-the-shelf reagents (zinc dust and ammonium formate) are employed, and the reaction is quite robust in not requiring dry solvents or special precautions.

E. Reductive Cyclization and Deoxygenation (5 → 6 → 1). In the previous synthesis,[1,2] nitrohexanone **5** was converted to *N*-oxide **6** using Zn in the presence of acetic acid. Such conditions are incompatible with a number of functional groups. In the synthesis of **1**, we were content to bypass the preparation of the *N*-oxide **6**. However, *N*-oxides are valuable intermediates in the syntheses of functionalized tetrahydrodipyrrins.[20] Accordingly, we investigated alternatives for the preparation and deoxygenation of *N*-oxide **6**. During the survey of conditions for conversion of **5** → **1**, we found that Zn/NH_4Cl in THF/H_2O preferentially gave the *N*-oxide **6** (Table 2, entries 10−17). For the preparative scale, nitrohexanone **5** was dissolved in THF/H_2O (1:1) and treated with Zn/NH_4Cl at 0 °C for 15 min. GC analysis showed 70% of *N*-oxide **6** and 19% of **1**. Chromatography afforded **6** in 66% yield. For the direct deoxygenation of *N*-oxide **6**, we examined a number of reagents ($InCl_3$, PPh_3/toluene, $(MeO)_3P$/toluene, CS_2, $HCOONH_4$/pivaloyl chloride, and $Zn/HCOONH_4$). Most of the methods caused extensive decomposition of **6** or no reaction. Again, the best result was obtained using $Zn/HCOONH_4$ in THF, affording **1** in 81% yield (Scheme 4).

II. Investigation of Multistep Transformations. Here we investigated a number of approaches to obtain intermediates or the target compound **1** in an expeditious manner.

A. Conversion of 2 → 4. Pyrrole-2-carboxaldehyde (**2**) in excess nitromethane was treated with *n*-propylammonium acetate, affording the crude 2-(2-nitrovinyl)pyrrole (**3**). Workup entailed diluting the crude mixture with CH_2Cl_2, removing the ammonium salt by washing with water, and removing excess nitromethane under high vacuum. The crude **3** was dissolved in $CHCl_3$/2-propanol (3:1) and treated with 2.0 mol equiv of $NaBH_4$ in the presence of silica, affording 2-(2-nitroethyl)pyrrole (**4**) in 40% yield (Scheme 5).

B. Conversion of 4 → 1. The conversion of 2-(2-nitroethyl)pyrrole (**4**) to the desired tetrahydrodipyrrin **1** was prompted by the observation that GC and TLC analyses of the crude reaction mixture following Michael addition of **4** and mesityl oxide did not show any significant side products. Therefore we employed a two-step, one-flask procedure entailing Michael addition followed by reduction of the crude nitrohexanone **5**. The crude reaction mixture was diluted with ethyl acetate and washed with water; the organic layer was dried; excess mesityl oxide was removed under high vacuum; and the resulting oil was subjected to reductive cyclization using $Zn/HCOONH_4$. The yield of **1** was 53% (Scheme 5).

C. Conversion of 2 → 5. The conversion of pyrrole-2-carboxaldehyde (**2**) to the nitrohexanone-pyrrole (**5**) was carried out by solventless condensation with nitromethane, reduction with $NaBH_4$, Michael addition with mesityl oxide, and workup including chromatography. The desired **5** was obtained in 29% yield (Scheme 5).

D. Conversion of 2 → 1. Taking together all improvements in each of the four steps, the direct conversion of pyrrole-2-carboxaldehyde (**2**) to **1** was investigated (Scheme 5). Treatment of a solution of **2** in $MeNO_2$ with propylammonium acetate afforded crude 2-(2-nitrovinyl)pyrrole **3**. After workup (dilution with CH_2Cl_2, washing with water, removal of excess $MeNO_2$ under high vacuum), the crude **3** was dissolved in $CHCl_3$/2-propanol, to which silica was added followed by $NaBH_4$ (2 mol equiv). After workup (filtration, concentration of the filtrate), the crude **4** (brown-greenish oil) was dissolved in excess mesityl oxide (1.5 equiv), excess DBU (3 equiv) was added, and the Michael addition was performed overnight at room temperature. After workup (dilution with ethyl acetate, washing with water and brine, removal of solvent and excess mesityl oxide under reduced pressure), the crude **5** was dissolved in THF (ACS grade) and treated with excess $Zn/HCOONH_4$ for 2 h. Workup (filtration, concentration of the filtrate, and chromatography on silica) afforded **1** as a light-brown solid in 22% overall yield. The tetrahydrodipyrrin obtained in this manner from **2** was slightly darker than upon synthesis from a pure sample of the immediate precursor **5**, although the ^1H NMR spectrum did not show any noticeable impurities.

The entire synthesis at the 60-mmol scale afforded 2.5 g of **1** (22% yield) in a 3-day period. The procedure at the 0.4 mol-scale provided ∼11 g of **1** (14.5% yield) in one batch, which is 22 times more than reported previously. Compound **1** gave satisfactory elemental analysis data in only one instance (upon preparation from **6**); in all other cases, all other characterization data were satisfactory, and samples of **1** were successfully employed in several syntheses of chlorins.

In summary, the valuable tetrahydrodipyrrin **1** can be obtained in a stepwise manner via streamlined procedures.

(20) Kim, H.-J. Ph.D. Thesis, North Carolina State University, 2005.

Table 2. **Conditions for the Reductive Cyclization (5 → 1)**

entry	Zn (equiv)	NH_4X (equiv)	solvent	temp, time	**5**:**6**:**1**[a]
1	15	$HCOONH_4$ (3)	MeOH	rt, 30 min	0:44:34
2	2	$HCOONH_4$ (15)	MeOH	rt, 30 min	0:42:40
3	15	$HCOONH_4$ (15)	MeOH	rt, 30 min	0:27:63
4	15	$HCOONH_4$ (15)	MeOH	rt, 2 h	0:5:68
5	15	$HCOONH_4$ (15)	MeOH	reflux, 20 min	0:0:51
6	15	$HCOONH_4$ (15)	MeCN	rt, 2 h	0:4:64
7	15	$HCOONH_4$ (15)	THF	rt, 2 h	1:0:76
8	15	$HCOONH_4$ (15)	ethyl acetate	rt, 2 h	0:18:54
9	15	$HCOONH_4$ (15)	CH_2Cl_2	rt, 2 h	0:37:48
10	15	NH_4Cl (3)	THF/H_2O, 1:1	rt, 30 min	0:61:21
11	15	NH_4Cl (3)	THF/H_2O, 1:1	rt, 1 h	0:65:22
12	15	NH_4Cl (6)	THF/H_2O, 1:1	rt, 30 min	2:70:23
13	25	NH_4Cl (3)	THF/H_2O, 1:1	rt, 30 min	2:68:17
14	15	NH_4Cl (3)	THF/H_2O, 1:1	reflux, 30 min	<1:66:25
15	15	NH_4Cl (3)	THF/ H_2O, 4:1	rt, 30 min	1:72:20
16	5	NH_4Cl (3)	THF/H_2O, 1:1	rt, 30 min	4:72:17
17	15	NH_4Cl (3)	MeOH/THF, 1:1	rt, 30 min	34:33:9

[a] Ratio determined by GC analysis. The data do not sum to 100% because of side products and/or impurities.

Scheme 5

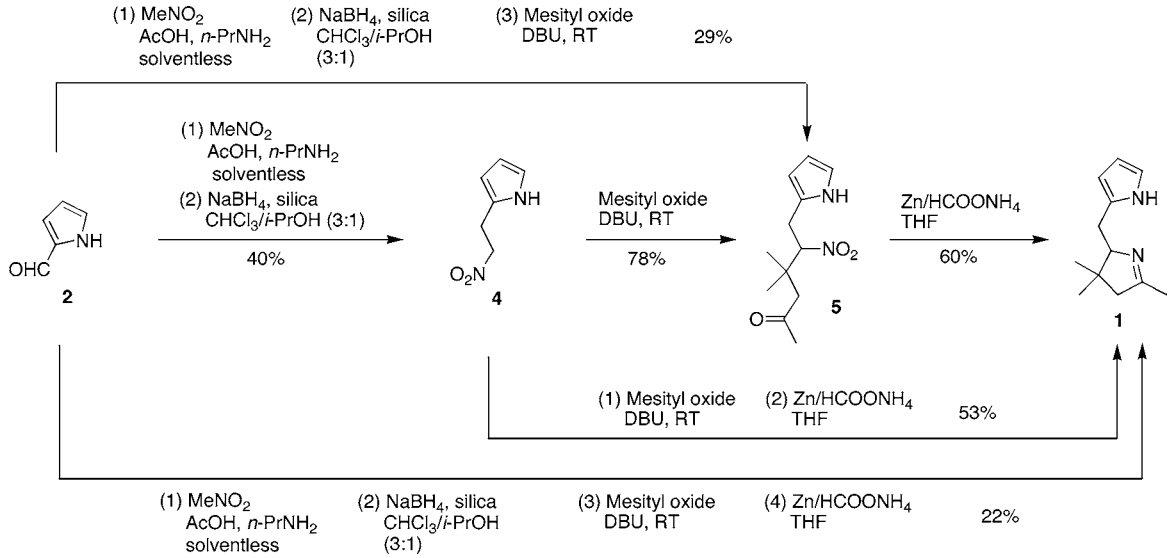


Table 3. **Comparison of routes for converting 2 → 1**

number of steps	isolated intermediates	duration[a] (day)	yield[b] (%)
5	**3**, **4**, **5**, **6**	10	11
4	**3**, **4**, **5**	9	17
3	**4**, **5**	7	19
2	**4**	5	21
1		3,[c] 4[d]	22,[c] 14.5[d]

[a] Estimated working days. [b] Overall yield based on the amount of starting material **2**. [c] 60 mmol scale. [d] 0.40 mol scale.

In addition, a straightforward method has been developed for the direct conversion of pyrrole-2-carboxaldehyde (**2**) to **1** that is relatively fast, affords reasonable overall yield, employs simple reagents and methods, and has limited reliance on chromatography. A comparison of the various routes for converting **2** → **1** is provided in Table 3. Taken together, the availability of expedient routes to multigram quantities of **1** should facilitate entry into numerous hydroporphyrin architectures.

Experimental Section

General. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were collected at room temperature in $CDCl_3$. Melting points are uncorrected. Column chromatography was performed with flash silica or alumina (80−200 mesh). The $CHCl_3$ contained 0.8% ethanol. All solvents and reagents were used as received. Zinc was employed in the form of zinc dust (<10 micron). In all cases when a salt (e.g., $HCOONH_4$) and zinc dust were added to a reaction mixture, the salt was added first. All procedures were performed at room temperature unless noted otherwise.

2-(2-Nitrovinyl)pyrrole (3). A stirred solution of acetic acid (2.00 mL, 35.0 mmol) in methanol (5 mL) under argon at 0 °C was treated dropwise with *n*-propylamine (2.71 mL, 33.0 mmol). The resulting *n*-propylammonium acetate solution was stirred at 0 °C for 5 min, then added dropwise to a

stirred solution of **2** (5.70 g, 60.0 mmol) in nitromethane (9.66 mL, 180 mmol) at 0 °C. The resulting mixture was stirred at 0 °C. After 15 min, the cooling bath was removed, and stirring was continued at room temperature. The color changed from yellow to dark orange during the course of reaction. After 2 h, CH_2Cl_2 (100 mL) was added, and the organic phase was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under high vacuum to afford an orange-brown solid. Filtration through a silica pad (CH_2Cl_2) afforded an orange solid, which was dissolved in a minimal volume of CH_2Cl_2 and precipitated with hexanes to afford orange crystals (3.93 g, 47%): mp 110−112 °C (lit.[1] 112−114 °C); ^{1}H NMR δ 6.38−6.40 (m, 1H), 6.81−6.83 (m, 1H), 7.12−7.13 (m, 1H), 7.48 (d, ^5J = 3.8 Hz, ^3J = 13.6 Hz, 1H), 7.99 (d, J = 13.6 Hz, 1H), 9.04−9.15 (br. s, 1H); ^{13}C NMR δ 112.9, 119.4, 124.1, 126.5, 129.9, 131.0. Anal. Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.31; H, 4.40; N, 20.22. FAB-MS obsd 139.0500, calcd 139.0508 [$(M + H)^+$, M = $C_6H_6N_2O_2$].

2-(2-Nitroethyl)pyrrole (4). Following a published procedure,[12] a solution of **3** (0.138 g, 1.00 mmol) in $CHCl_3$ (9.0 mL) and 2-propanol (3.0 mL) was treated with silica (1.2 g). The resulting suspension was treated in one portion with $NaBH_4$ (0.0760 g, 2.00 mmol) under vigorous stirring. The mixture was stirred at room temperature for 20 min, accompanied by a color change from deep yellow to pale brown. The mixture was filtered. The filter cake was washed with CH_2Cl_2. The combined filtrate was concentrated. The resulting oil was dissolved in CH_2Cl_2. The organic solution was washed with water and brine. The organic layer was dried (Na_2SO_4), concentrated, and subjected to high vacuum to remove traces of 2-propanol. The residue was dissolved in a small quantity of CH_2Cl_2 and filtered through a silica pad (CH_2Cl_2) to afford a pale yellow oil (0.106 g, 76%): ^{1}H NMR data were consistent with previously reported values;[2] ^{1}H NMR δ 3.31 (t, J = 6.8 Hz, 2H), 4.60 (t, J = 6.8 Hz, 2H), 6.00−6.09 (m, 1H), 6.14−6.18 (m, 1H), 6.71−6.73 (m, 1H), 8.20−8.24 (br, 1H); ^{13}C NMR δ 25.6, 75.5, 107.0, 108.9, 118.0, 126.1. Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.54; H, 5.88; N, 19.84.

4,4-Dimethyl-5-nitro-6-(1*H*-pyrrol-2-yl)hexan-2-one (5). A mixture of **4** (1.40 g, 10.0 mmol) and mesityl oxide (1.26 mL, 11.0 mmol) was treated with DBU (4.57 g, 30.0 mmol). The temperature rose immediately, and the reaction mixture darkened. The reaction mixture was stirred at room temperature for 24 h, diluted with ethyl acetate (100 mL), and washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated. Excess mesityl oxide was removed under high vacuum. The resulting oil was dissolved in a minimal amount of CH_2Cl_2 and filtered through a silica pad [ethyl acetate/hexanes (1:3)] to afford a light brown oil which solidified to a light-brown solid (1.85 g, 78%): mp 59−61 °C (lit.[2] 54−55 °C); ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.25 (s, 3H), 2.14 (s, 3H), 2.41 (AB, J = 17.4 Hz, 1H), 2.59 (AB, J = 17.4 Hz, 1H), 3.04 (ABX, ^3J = 2.4 Hz, ^2J = 15.6 Hz, 1H), 3.35 (ABX, ^3J = 11.6 Hz, ^2J = 15.6 Hz, 1H), 5.13 (ABX, ^3J = 2.4 Hz, ^2J = 11.6 Hz, 1H), 5.95−5.99 (m, 1H), 6.08−6.10 (m, 1H), 6.65−6.67 (m, 1H), 8.10−8.13 (br s, 1H); ^{13}C NMR δ 24.3, 24.6, 26.8, 32.1, 36.9, 51.6, 94.9, 107.5, 108.9, 118.0, 126.2, 207.2. Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.42; H, 7.61; N, 11.48.

Screening Protocol for Reductive Cyclization of 5. Reactions were done at the 0.1-mmol scale. Compound **5** was stirred in an appropriate solvent (0.2 mL) in the presence of the reagents for reductive cyclization for the given time. The reaction mixture was diluted with ethyl acetate (2 mL), filtered through a plug of cotton, and analyzed by GC.

2,3,4,5-Tetrahydro-1,3,3-trimethyldipyrrin *N*-Oxide (6). A mixture of **5** (2.38 g, 10.0 mmol), THF (25 mL), and water (25 mL) was treated with NH_4Cl (1.60 g, 30.0 mmol) and zinc dust (9.80 g, 150 mmol) at 0 °C. The resulting suspension was stirred vigorously at 0 °C for 15 min and then was diluted with ethyl acetate and filtered. The filter cake was washed with ethyl acetate. The combined filtrate was washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated under vacuum. The resulting oil was chromatographed [silica, ethyl acetate then CH_2Cl_2/MeOH (10:1)] to afford a pale yellow oil which solidified to a white solid (1.36 g, 66%): mp 99−102 °C (lit.[4] 85−87 °C); ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.19 (s, 3H), 2.05−2.06 (m, 3H), 2.27−2.32 (m, 1H), 2.42−2.48 (m, 1H), 2.98−3.08 (m, 2H), 3.88−3.91 (m, 1H), 5.93−5.94 (m, 1H), 6.06−6.08 (m, 1H), 6.69−6.70 (m, 1H), 10.55−10.65 (br, 1H); ^{13}C NMR δ 13.5, 23.0, 25.8, 27.9, 37.3, 47.2, 81.3, 106.3, 107.4, 117.6, 128.9; FAB-MS obsd 207.1479, calcd 207.1497 [$(M + H)^+$, M = $C_{12}H_{18}N_2O$].

2-(1,3-Dinitroprop-2-yl)pyrrole (8). A small sample was isolated from the reaction of pyrrole-2-carboxaldehyde with excess nitromethane, as an orange oil. Limited data were obtained: ^{1}H NMR δ 4.34−4.41 (m, 1H), 4.70−4.79 (m, 5H), 6.05−6.07 (m, 1H), 6.15−6.17 (m, 1H), 6.73−6.75 (m, 1H), 8.30−836 (br s, 1H); ^{13}C NMR δ 35.4, 76.4, 106.9, 109.5, 119.3, 124.5.

2,3,4,5-Tetrahydro-1,3,3-trimethyldipyrrin (5 → 1). A stirred suspension of $HCOONH_4$ (9.45 g, 150 mmol) and nitrohexanone **5** (2.38 g, 10.0 mmol) in THF (40 mL) was treated in one portion with zinc dust (9.76 g, 150 mmol). The resulting mixture was stirred vigorously at room temperature. After 2 h, ethyl acetate (40 mL) was added, and the mixture was filtered. The filter cake was washed with ethyl acetate. The filtrate was washed with water and brine and dried (Na_2SO_4). The solvent was concentrated to afford a light brown oil, which slowly solidified upon standing. The crude product (1.65 g) was chromatographed (silica, ethyl acetate) to afford a light brown oil which solidified to a pale yellow-orange solid (1.15 g, 60%): mp 55−56 °C (lit.[2] 53−54 °C); ^{1}H NMR δ 0.96 (s, 3H), 1.13 (s, 3H), 2.05−2.06 (m, 3H), 2.31 (AB, J = 16.8 Hz, 1H), 2.39 (AB, J = 16.8 Hz, 1H), 2.62 (ABX, ^3J = 11.6 Hz, ^2J = 14.8 Hz, 1H), 2.80 (ABX, ^3J = 3.2 Hz, ^2J = 14.8 Hz, 1H), 3.64−3.67 (m, 1H), 5.95−5.97 (m, 1H), 6.11−6.13 (m, 1H), 6.70−6.72 (m, 1H), 9.75−9.83 (br. s, 1H); ^{13}C NMR δ 20.6, 23.0, 27.4, 28.1, 42.0, 54.4, 80.4, 105.3, 107.4, 116.5, 131.8, 174.6; FAB-MS obsd 191.1534, calcd 191.1548 [$(M + H)^+$, M = $C_{12}H_{18}N_2$].

2,3,4,5-Tetrahydro-1,3,3-trimethyldipyrrin (6 → 1). A solution of **6** (1.03 g, 4.99 mmol) in THF (20 mL) was treated with $HCOONH_4$ (4.78 g, 75.0 mmol) and zinc dust (4.88 g, 74.7 mmol). The resulting suspension was stirred at room temperature. After 2 h the mixture was diluted with ethyl acetate and filtered. The filter cake was washed with ethyl acetate. The combined filtrate was washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated. The resulting oil was chromatographed (silica, ethyl acetate) to afford a yellow oil which solidified to white crystals (0.62 g, 81%): the ^1H and ^{13}C NMR spectra were identical as described above; mp 52−53 °C (lit.[4] 53−54 °C). Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H 9.53; N, 14.72. Found: C, 75.61; H, 9.71; N, 14.63.

Direct Conversion of 2 → 4. A stirred solution of acetic acid (2.00 mL, 35.0 mmol) in methanol (5 mL) under argon at 0 °C was treated dropwise with *n*-propylamine (2.71 mL, 33.0 mmol). The resulting *n*-propylammonium acetate mixture was stirred at 0 °C for 5 min, then added dropwise to a stirred solution of **2** (5.70 g, 60.0 mmol) in nitromethane (9.66 mL, 180 mmol) at 0 °C. The resulting mixture was stirred at 0 °C. After 15 min, the cooling bath was removed, and stirring was continued at room temperature. The color changed from yellow to dark orange during the course of reaction. After 2 h (see note below), CH_2Cl_2 (100 mL) was added, and the organic phase was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under high vacuum to afford an orange-brown solid. The crude 2-(2-nitrovinyl)pyrrole was dissolved in a mixture of $CHCl_3$ (300 mL) and 2-propanol (100 mL), to which silica (72 g) was added. The mixture was stirred vigorously, and $NaBH_4$ (4.54 g, 120 mmol) was added in one batch. After 30 min, TLC analysis showed complete consumption of the starting 2-(2-nitrovinylpyrrole). The mixture was filtered. The filter cake was washed with CH_2Cl_2. The filtrate was concentrated, and the resulting dark oil was filtered through a silica pad (CH_2Cl_2) to afford an orange oil (3.52 g, 40%). The ^1H NMR data were consistent with reported values.[2]

Note: The time for completion of the reaction varied from 1 to 3 h. It is recommended to monitor the progress of the reaction with TLC and carry out the workup immediately upon disappearance of the starting material.

Direct Conversion of 2 → 5. A stirred solution of acetic acid (2.00 mL, 35.0 mmol) in methanol (5 mL) under argon at 0 °C was treated dropwise with *n*-propylamine (2.71 mL, 33.0 mmol). The resulting *n*-propylammonium acetate mixture was stirred at 0 °C for 5 min and then added dropwise to a stirred solution of **2** (5.70 g, 60.0 mmol) in nitromethane (9.66 mL, 180 mmol) at 0 °C in a 100 mL flask. The resulting mixture was stirred at 0 °C. After 15 min, the cooling bath was removed, and the stirring was continued at room temperature for 2 h. CH_2Cl_2 (100 mL) was added, and the organic phase was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under high vacuum to afford a brownish oil. The brownish oil was placed in a 1 L flask, and a mixture of $CHCl_3$ (300 mL) and 2-propanol (100 mL) was added, followed by silica (72 g). The mixture was stirred vigorously, and $NaBH_4$ (4.54 g, 120 mmol) was added in one batch. After 1 h, TLC analysis showed the presence of starting material. Hence, another batch of $NaBH_4$ (2.80 g, 74.0 mmol) was added, and stirring was continued. After 2 h, TLC analysis showed the complete consumption of starting material, and GC analysis showed the formation of **4**. The mixture was filtered, and the filter cake was washed with CH_2Cl_2. The filtrate was concentrated. The resulting dark oil was dissolved in mesityl oxide (20 mL), and then DBU (13.7 g, 90.0 mmol) was added. The resulting solution was stirred for 13 h. The crude product was then filtered through a silica pad [ethyl acetate/hexanes (1:3)] to afford a light brown oil (4.2 g, 29%): ^1H NMR data were consistent with values reported above. Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.73; H, 7.79; N, 11.83.

Direct Conversion of 4 → 1. A solution of **4** (2.10 g, 15.0 mmol) in mesityl oxide (2.83 mL, 22.5 mmol) was treated with DBU (6.86 g, 45.0 mmol). The resulting dark mixture was stirred for 14 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated. Excess mesityl oxide was removed under high vacuum. The resulting brown oil was dissolved in THF (40 mL), and then $HCOONH_4$ (14.2 g, 225 mmol) and zinc dust (17.7 g, 225 mmol) were added. The resulting mixture was stirred vigorously at room temperature. After 2 h, GC analysis showed complete consumption of hexanone **5** and *N*-oxide **6**. Ethyl acetate (50 mL) was added, and the mixture was filtered through filter paper. The filter cake was washed with ethyl acetate. The combined filtrate was washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated. The resulting oil was chromatographed (silica, ethyl acetate) to afford a brown oil which solidified to a pale brown solid (1.51 g, 53%). The characterization data (mp, ^1H NMR, ^{13}C NMR, and FAB-MS) were consistent with values reported above.

Direct Conversion of 2 → 1 (60 mmol Scale). A stirred solution of acetic acid (2.00 mL, 35.0 mmol) in methanol (5 mL) under argon at 0 °C was treated dropwise with *n*-propylamine (2.71 mL, 33.0 mmol). The resulting *n*-propylammonium acetate solution was stirred at 0 °C for 5 min and then added dropwise to a stirred solution of **2** (5.70 g, 60.0 mmol) in nitromethane (9.66 mL, 180 mmol) at 0 °C. The resulting mixture was stirred at 0 °C. After 15 min, the cooling bath was removed, and stirring was continued at room temperature. The color changed from yellow to dark orange during the course of the reaction. After 2 h (Note 1), CH_2Cl_2 (100 mL) was added, and the organic phase was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under high vacuum to afford an orange oil that solidified to give an orange-brown solid. The crude 2-(2-nitrovinyl)pyrrole was dissolved in a mixture of $CHCl_3$ (300 mL) and 2-propanol (100 mL), to which silica (72 g) was added. The mixture was stirred vigorously, and $NaBH_4$ (4.54 g, 120 mmol) was added in one batch. After 30 min, TLC analysis showed complete consumption of the starting 2-(2-nitrovinyl)pyrrole. The mixture was filtered. The filter cake was washed with CH_2Cl_2. The filtrate was

concentrated. The resulting dark oil was dissolved in mesityl oxide (20 mL), and then DBU (13.7 g, 90.0 mmol) was added. The resulting dark solution was stirred for 14 h. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated. Excess mesityl oxide was removed under high vacuum, followed by entrainment with hexanes (2×). The resulting brown oil was dissolved in THF (160 mL), and then $HCOONH_4$ (37.8 g, 600 mmol) and zinc dust (39.2 g, 600 mmol) were added. The resulting mixture was stirred vigorously at room temperature. After 3 h, GC analysis did not show the presence of hexanone **5** and *N*-oxide **6**. Ethyl acetate (200 mL) was added, and the mixture was filtered through Celite. The filter cake was washed with ethyl acetate. The combined filtrate was washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated. The resulting oil was chromatographed (silica, ethyl acetate) to afford a brown oil which solidified to a pale brown solid (2.54 g, 22%). The characterization data (mp, ^{1}H NMR, FAB-MS data) were consistent with those described above.

Direct Conversion of 2 → 1 (0.40 mol Scale). A mixture of acetic acid (12.9 mL, 225 mmol) in MeOH (20 mL) was treated dropwise with *n*-propylamine (16.44 mL, 200.0 mmol) at 0 °C (see note i below). The resulting mixture was stirred at room temperature for 15 min and then transferred to the solution of pyrrole-2-carboxaldehyde (38.0 g, 0.400 mol) in $MeNO_2$ (64.5 mL, 1.20 mol) under argon at 0 °C. The mixture was stirred at room temperature until TLC showed complete consumption of the starting aldehyde (∼5 h, see note ii below). Excess $MeNO_2$ was removed under high vacuum (water bath, 40 °C). The resulting oil was triturated with hexanes (50 mL), and the volatile components were evaporated. This procedure was repeated three times. The resulting brown oil was dissolved in $CHCl_3$ and filtered through a pad of silica (3 cm × 7 cm). The filter cake was washed with $CHCl_3$ (the total volume of solvent used was 2000 mL, see note iii below). The filtrate was transferred to a 5 L flask. 2-Propanol (667 mL) and silica (480 g) were added. Under vigorous stirring, $NaBH_4$ (38 g, 1.0 mmol) was added over the course of 1 min. The mixture was stirred for 45 min, then another batch of $NaBH_4$ (10.0 g, 264 mmol) was added and stirring was continued for 75 min. TLC showed complete consumption of 2-(2-nitrovinyl)pyrrole (**3**). The mixture was filtered through filter paper and the filter cake was washed with CH_2Cl_2 (∼4000 mL). The filtrate was concentrated to afford a dark brown oil. The resulting crude 2-(2-nitroethyl)pyrrole (**4**) was dissolved in mesityl oxide (130 mL, 1.13 mol). DBU (91.0 g, 598 mmol) was added, and the mixture was stirred overnight. Ethyl acetate (500 mL) was added, and the mixture was washed with water (3 × 200 mL) and brine (100 mL). The organic phase was dried (Na_2SO_4). Removal of the solvent and excess mesityl oxide under high vacuum afforded crude **5** as a brown oil. The crude oil was dissolved in THF (1000 mL), and the resulting solution was transferred to a three-necked 2-L flask. $HCOONH_4$ (252 g, 3.90 mol) and zinc dust (261 g, 3.90 mol) were added, and the resulting suspension was vigorously stirred using a mechanical stirrer (see note iv below). After 2 h, GC analysis did not show any starting hexanone (**5**) or intermediate *N*-oxide (**6**). The mixture was filtered through filter paper, and the filter cake was washed with ethyl acetate (2500 mL). The filtrate was concentrated to afford a brown solid. The brown solid was chromatographed (6 cm × 22 cm, 260 g of silica) using ethyl acetate (3000 mL, ∼8 h), affording a brown oil which slowly crystallized to a pale brown solid (8.80 g). The mixed fractions were rechromatographed on a small silica column to afford an additional 2.26 g of title compound (total yield 11.06 g, 14.5%; see note v below). The characterization data (mp, ^{1}H NMR, FAB-MS data) were consistent with those described above.

Notes:

(i) Excess acetic acid is necessary because the use of equimolar amounts of AcOH and propylamine in some experiments causes extensive decomposition of starting material.

(ii) The time for completion of the reaction varied from 4 to 7 h. It is recommended to monitor the progress of the reaction with TLC and carry out the workup immediately upon disappearance of the starting material.

(iii) Alternatively, the reaction mixture was diluted with CH_2Cl_2 (∼300 mL) and washed with water and brine. The organic phase was dried (Na_2SO_4). The CH_2Cl_2 was removed under low vacuum, and then excess $MeNO_2$ was removed under high vacuum (water bath, 40 °C). The resulting oil was triturated with hexanes (50 mL), and the volatile components were removed. This procedure was repeated three times. The resulting brown-orange solid was subjected to reduction as described above.

(iv) The reductive cyclization was done under heterogeneous conditions and required a large amount of solid material (Zn/$HCOONH_4$). The heterogeneous mixture caused difficulties in stirring, which affected the reaction time required for completion. A mechanical stirrer is recommended for effective stirring.

(v) Most intermediates (especially **3** and **4**) were relatively unstable upon standing in the crude reaction mixtures; therefore, all operations as well as subsequent reaction steps should be carried out promptly.

Acknowledgment

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

Supporting Information Available

Tables of data for survey reactions; ^{1}H NMR spectral data for **1** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review June 2, 2005.

OP050087E