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Studies in Chlorin Chemistry. II. A Versatile Synthesis of Dihydrodipyrrins

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15 **16** **8**

Dihydrodipyrrins are key building blocks for the synthesis of hydroporphyrins, many of which have important biological activity. The title compounds were prepared in stereo- and regioselective fashion by a three-step sequence consisting of (1) Pd(0)-catalyzed coupling-cyclization of 2-iodopyrroles with γ-alkynoic acids to afford enelactones of the desired substitution pattern, (2) methylenation at the lactone carbonyl group employing the Petasis reagent, and (3) in situ enol-ether hydrolysis and amination of the resultant 1,4-diketone to close the pyrroline ring (nine examples). Yields for each step were generally high, although in substrates not blocked by geminal substitution aromatization to a dipyrromethane is a competing side reaction.

Introduction

Hydroporphyrins are partly reduced derivatives of the porphyrin ring system, the most common of which are members of the chlorin (**1a**, $\Delta_{7,8,12,13}$), isobacteriochlorin (**1b**, $\Delta_{12,13}$), and bacteriochlorin (**1c**, $\Delta_{7,8}$) families (Figure 1; Δ signifies the location of double bonds).[1] Aromatic tetrapyrroles of type **1a**−**c** have diverse functions in nature. Representative examples include chlorophyll *a*, the ubiquitous chlorin that regulates photosynthesis in green plants, algae, and cyanobacteria; bonellin (**2**), the sex-differentiating chlorin of the marine worm *Bonella viridis*;[2] and siroheme (**3**), the isobacteriochlorin prosthetic group of numerous sulfite and nitrite reductases.[3] In its reduced Fe-free form, **3** is also a key intermediate in vitamin B_{12} biosynthesis.[4] A number of hydroporphyrins are also of medical interest. These include members of the chlorin and bacteriochlorin families, which because of their favorable photophysical properties are attractive agents in tumor photodynamic therapy (PDT). This technique employs photostimulated production of singlet oxygen to selectively eradicate malignant tissue.[5] In a nonrelated area, bacteriochlorins of the tolyporphin (**4**)

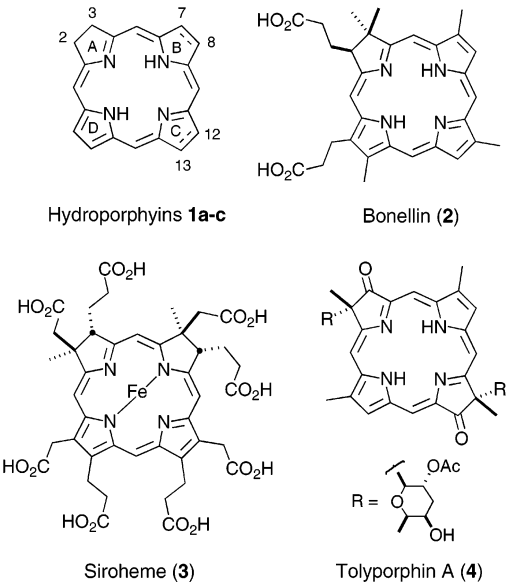

FIGURE 1. Some naturally occurring hydroporphyrins.

(1) (a) Battersby, A. R. *Nat. Prod. Rep.* **2000**, *17*, 507. (b) Montforts, F.-P.; Gerlach, B.; Höper, F. *Chem. Rev.* **1994**, *94*, 327.
(2) Agius, L.; Ballantine, J. A.; Ferrito, V.; Jaccarini, V.; Murray-Rust, P.; Pelter, A.; Psaila, A. F.; Schembri, P. J. *Pure Appl. Chem.* **1979**, *51*, 1847.
(3) (a) Murphy, M. J.; Siegel, L. M. *J. Biol. Chem.* **1973**, *248*, 6911. (b) Murphy, M. J.; Siegel, L. M.; Tove, S. R.; Kamin, H. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 612.
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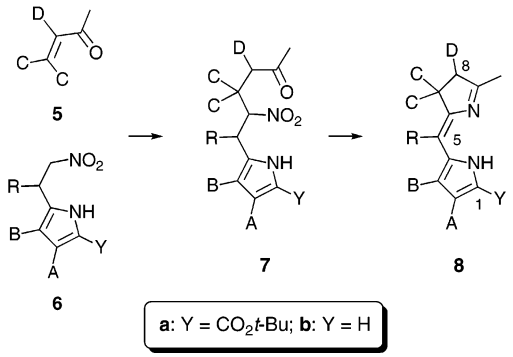
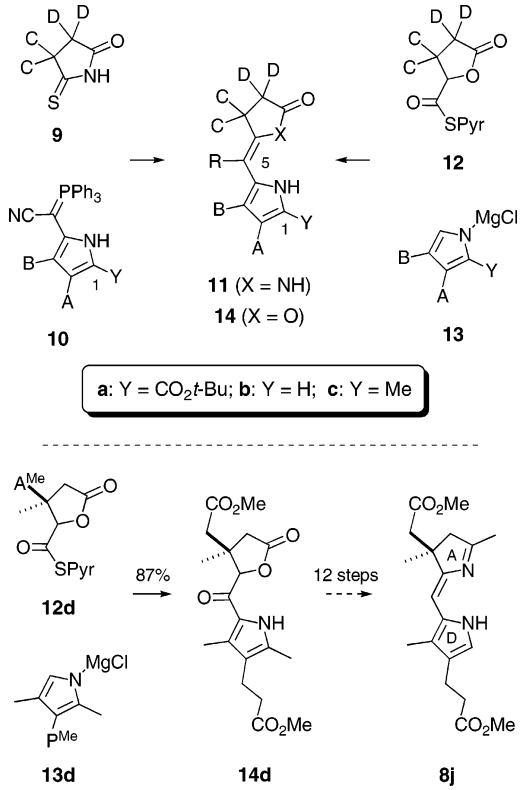
SCHEME 1



class have been shown to reverse tumor multidrug resistance (MDR) and may find use in cancer chemotherapy.[6]

In contrast to chlorophyll *a*, most naturally occurring hydroporphyrins are available only in exceedingly small quantities, which contributes to their continuing interest as synthetic targets. Many de novo syntheses of **1a**−**c** employ dihydrodipyrrin intermediates of type **8**, which function as either "western" A,D- or "northern" A,B-ring building blocks (Scheme 1). The earliest and still most frequently applied syntheses of **8** involve reductive cyclization of nitroketones of general structure **7**, themselves prepared by Michael addition of enones **5** with pyrrole derivatives **6**.[7] Battersby in particular has made elegant use of this strategy in a number of chlorin and isobacteriochlorin syntheses, as well as in biosynthetic studies on vitamin B_{12}.[7a−c] More recently, Lindsey et al. have adapted this approach to the synthesis of chlorins bearing peripheral synthetic "handles".[7c,d] Typically, conjugate addition of **6a** or **6b** with mesityl oxide (**5**, C = Me, D = H), followed by reductive cyclization, affords dihydrodipyrrins **8a**,**b** (C = Me, D = H) in 15−40% overall yields.[7] The relatively modest yields for this sequence are mainly due to difficulty controlling the key reductive cyclization of **7** to **8**, which invariably affords products contaminated by over-reduction at C_5−C_6. This problem is partly addressed by reoxidation of the derived tetrahydrodipyrrins employing $Pb(OAc)_4$, although chemoselectivity is generally poor.[7a,8] A more satisfactory solution is to employ the C_5−C_6-reduced form of dihydrodipyrrins **8** to prepare tetrahydrobilenes, at which point oxidation can be effected concomitant with ring closure.[7f] In either case, the choice of groups C is very limited and C_8 must be monosubstituted. Finally, this methodology fails for C_5-meso-substituted dihydrodipyrrins (i.e., R ≠ H).[8]

SCHEME 2



Several strategies have been explored in attempts to develop more general syntheses of dihydrodipyrrins **8**. Building upon earlier studies by Gossauer,[9] Battersby et al. showed that monothioimide derivatives of type **9** undergo condensation with cyano-stabilized Wittig reagents **10** to afford variable yields of dihydropyrromethenones **11** (R = CN, X = NH; Scheme 2).[10]

These last materials were then converted to dihydrodipyrrins **8** by a seven-step sequence initiated by removal of the *meso*-cyano group.[11] Among other examples, this strategy was employed in an enantioselective synthesis of the Fe-free form of siroheme (**3**), in which the monothioimide starting material was prepared by either of two routes: oxidative degradation of vitamin B_{12}[12] or in a 12-step sequence starting with *R*-malic acid.[13] In large part the success of this strategy depends on the availability of monothioimides **9**, which even in simple cases are difficult to prepare in regioselective

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(6) Prinsep, M. R.; Caplan, F. R.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Am. Chem. Soc.* **1992**, *114*, 385.

(7) (a) Harrison, P. J.; Sheng, Z.-C.; Fookes, C. J. R.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1667. (b) Battersby, A. R.; Cutton, C. J.; Fookes, C. J. R.; Turner, S. P. D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1557. (c) Battersby, A. R.; Dutton, C. J.; Fookes, C. J. R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1569. (d) Strachan, J.-P.; O'Shea, D. F.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 3160. (e) Balasubramanian, T.; Strachan, J.-P.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7919. (f) Taniguchi, M.; Ra, D.; Mo, G.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2001**, *66*, 7342.

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(9) Gossauer, A.; Hinze, R.-P. *J. Org. Chem.* **1978**, *43*, 283.

(10) (a) Arnott, D. M.; Battersby, A. R.; Harrison, P. J.; Henderson, G. B.; Sheng, Z.-C. *J. Chem. Soc., Chem. Commun.* **1984**, 525. (b) Battersby, A. R.; Turner, S. P. D.; Block, M. H.; Sheng, Z.-C.; Zimmerman, S. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1577. (c) Arnott, D. M.; Harrison, P. J.; Henderson, G. B.; Sheng, Z.-C.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 265.

(11) Battersby, A. R.; Block, M. H.; Leeper, F. J.; Zimmerman, S. C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2189.

(12) Block, M. H.; Zimmerman, S. C.; Henderson, G. B.; Turner, S. P. D.; Westwood, S. W.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Chem. Commun.* **1985**, 1061.

(13) Whittingham, W. G.; Ellis, M. K.; Guerry, P.; Henderson, G. B.; Müller, B.; Taylor, D. A.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Chem. Commun.* **1989**, 1116.

fashion. In view of this difficulty, and also because of the excessive number of manipulations following coupling, the authors later characterized this approach as "experimentally very demanding" and not suitable for larger-scale preparations.[14]

In follow-up studies the Battersby group showed that *S*-pyridylthioesters **12** undergo clean condensation with pyrrole Grignard reagents of type **13c** (Y = Me), affording good to excellent yields of acyl lactones **14c** (Scheme 2; R = OH, X = O, Y = Me). Unfortunately, though, it proved impossible to employ Grignard reagents **13a**,**b** having Y = CO_2t-Bu or H. This limitation necessitated extensive modifications to both the C_1- and C_5-substituents in **14c** before ultimate conversion to dihydrodipyrrins **8**. In a noteworthy example of this methodology, Battersby et al. developed a 14-step synthesis of the chiral thioester derivative **12d** beginning with L-glutamic acid (Scheme 2).[14,15] Thioester **12d** was then converted in 13 steps to the dihydrodipyrrin **8j**, which was a key intermediate in their synthesis of haem d_1.

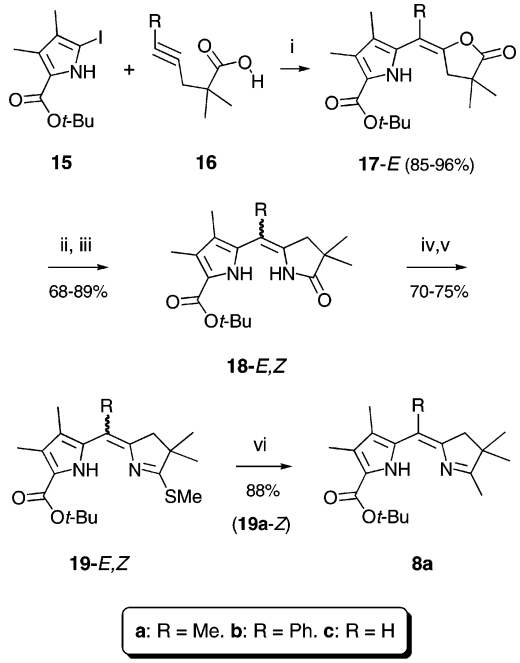
In this article, we describe a versatile synthesis of dihydrodipyrrins that is regio- and stereoselective, accommodates a wide variety of pyrrole- and meso-substituents, and can be adapted to prepare homochiral dihydrodipyrrins.

Results and Discussion

Method A. In a recent article, we described efficient syntheses of *E*-enelactones **17**-*E*, which were prepared in 85−96% yield by Pd(0)-catalyzed coupling/cyclization of iodopyrrole **15** with alkyne acids **16** (Scheme 3).[16] Lactones **17**-*E* were subsequently converted to *E*,*Z*-mixtures of thioimidates **19** by a four-step sequence involving aminolysis/cyclodehydration to afford lactams **18**, followed by thiolactam formation and S-methylation.[16b] We intended to convert both isomers of thioimidates **19** to the corresponding dihydrodipyrrins **8**, potential intermediates in a new chlorin synthesis. Following this strategy, methylation of **19a**-*Z* with the reagent system Pd(0)/MeZnI gave an 88% yield of **8a** as a single isomer. Surprisingly, however, **19a**-*E* failed to react under these conditions and many others.

Eventually this difference was traced to a selective activating effect of Zn, which serves to polarize the thioimidate C−S bond in **19a**-*Z* by chelation (Figure 2).[17] Control experiments showed that such activation is necessary for oxidative insertion of Pd(0). Chelation of this type is not possible for **19a**-*E*, which is also sterically prohibited from simple complexation (cf. Zn-**19**-*E*; for a detailed discussion of this mechanism see ref 17). Consequently, the desired cross-coupling reaction fails. Compounding this problem, the ratio of **19**-*Z*:**19**-*E* decreases

SCHEME 3[a]



[a] Reagents and conditions: i. $Pd(PPh_3)_4$, $BnNEt_3Cl$, CH_3CN, NEt_3, reflux. ii. NH_3, THF,-33°C to room temperature; iii. Montmorillonite K-10, THF, room temperature. iv. Lawesson's reagent, toluene, 100°C. v. MeI, THF, reflux. vi. ZnI_2, THF, MeMgBr, room temperature, then **19a**-*Z*, $PdCl_2(PPh_3)_2$, 70°C.

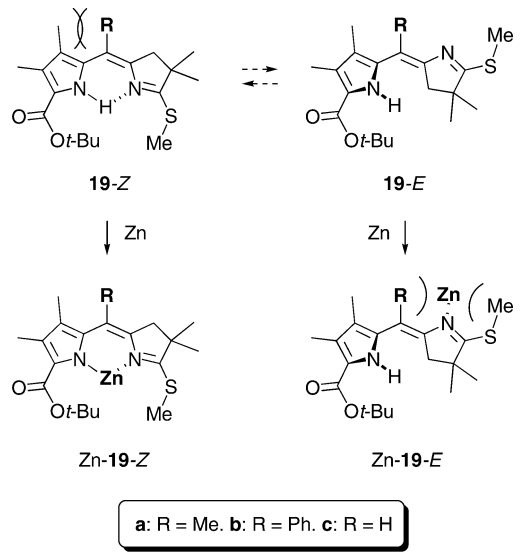


FIGURE 2. Selective Zn(2) activation of **19a**-*Z* (R = Me).

with increasing size of the meso-substituent (i.e., H > Me ≫ Ph), making it impractical to incorporate larger alkyl groups. This is because with small R-groups the planar *Z*-configuration is stabilized by hydrogen bonding,[17] but as R increases in size this effect becomes less important. In contrast, the twisted *E*-isomer **19**-*E* can accommodate large meso-substituents with minimal nonbonded interactions (in a closely related example the rings are skewed by 52°; cf. ref 17). For R = H the *Z*-thioimidate **19c**-*Z* is obtained nearly exclusively by the route outlined in Scheme 3, while for R = Ph the *E*:*Z* ratio approaches 50:50. Unfortunately, under the cou-

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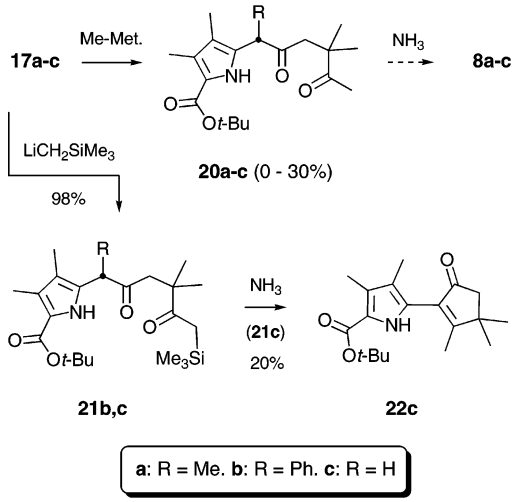
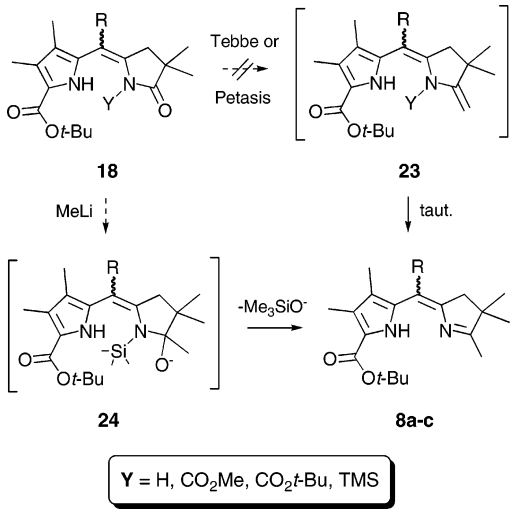
(16) (a) Jacobi, P. A.; Lanz, S.; Ghosh, I.; Leung, S. H.; Lower, F.; Pippin, D. *Org. Lett.* **2001**, *3*, 831. (b) Enelactones **17** are obtained exclusively as the *E*-isomers under kinetic control, as dictated by mechanistic considerations.[17] The stereochemistry of lactams **18** and thioimidates **19** depends mainly upon steric factors (cf. Figure 2). Dihydrodipyrrins **8** generally strongly favor the *Z*-stereochemistry due to intramolecular H-bonding.

(17) Ghosh, I.; Jacobi, P. A. *J. Org. Chem.* **2002**, *67*, 9304.

SCHEME 4



SCHEME 5



pling conditions **19**-*Z* and **19**-*E* do not equilibrate. With an unavoidable loss of material at such a late stage we set out to develop a more efficient synthesis of dihydrodipyrrins **8**.

Method B. In principle, dihydodipyrrins **8a**−**c** might be prepared in a more direct fashion by condensation of ammonia with diketones **20a**−**c**, themselves obtained by ring opening of enelactones **17a**−**c** with methyl anion or an equivalent species (Scheme 4). This approach was explored extensively with MeLi and MeMgBr but with little success. Invariably these reactions gave a complex mixture of multiple addition products containing only small amounts of the desired diketones **20**. Somewhat better results were obtained with sterically hindered nucleophiles, including lithiotrimethylsilylmethane ($LiCH_2SiMe_3$). This reagent is known to convert secondary and tertiary esters to methyl ketones,[18] and it gave essentially quantitative yields of trimethylsilyl ketones **21b**,**c** upon reaction with enelactones **17b**,**c**. Unfortunately, though, these key intermediates were relatively unstable, especially with respect to intramolecular aldol condensation. Compound **21c** (R = H), for example, produced significant quantities of cyclopentenone **22c** upon attempted ring closure with a variety of ammonia sources. The aldol reaction pathway appears to be facilitated by the TMS group, since the parent methyl ketones **20**, once formed, are relatively easy to handle (vide infra). Most likely this is due to Si-assisted dehydration of the initial aldol product, for which there is ample precedent (see also Scheme 5).[19] Finally, since the use of such highly nucleophilic reagents might be incompatible with substrates containing other ester groups, this route was put aside.

Method C. We also explored the possibility that enelactams **18** might be directly converted to dihydrodipyrrins **8** by methylenation followed by tautomerization (Scheme 5, **18** → **23** → **8**). A number of closely related transformations have been reported with both amides and lactams, although activation by N-substitution is usually required.[20] In the present case unsubstituted lactams **18** (Y = H) were either unreactive or suffered slow decomposition employing either the Petasis reagent ($TiCp_2Me_2$)[21] or the generally more reactive Tebbe reagent [$Cp_2TiCH_2ClAl(CH_3)$].[22] The most effective lactam activating groups are reported to be methyl- and *tert*-butylcarbamates,[20a] and we therefore prepared the corresponding enelactams **18** with Y = CO_2Me and Y = CO_2t-Bu. In both cases, these materials were difficult to access because of competing reaction at the pyrrole nitrogen. In any event modifications of this type were not productive since we still could detect no formation of enamines **23**. Finally, we made many efforts to prepare N-trimethylsilylated derivatives **18** where Y = TMS, since lactams of this type are known to undergo Petterson-like olefination with MeLi (i.e., **18** → **24** → **8**).[23] Unfortunately, however, these attempts were uniformly unsuccessful, perhaps due to steric hindrance.

Method D. In contrast to the low reactivity of enelactams **18**, ene*lactones* **17** were excellent substrates for methylenation (Scheme 6). This transformation was first accomplished employing the Tebbe reagent, in which case it was best to directly hydrolyze the crude enol ethers **25** using a biphasic system of dichloromethane and 50% aqueous TFA. Partly this was because of the cumbersome workup involved in isolating **25**. Nevertheless, on relatively small scales this procedure routinely afforded overall yields of 80−85% in the conversion of lactone **17a** to diketone **20a**. Similar results were obtained with the Petasis reagent, which in our experience is more easily prepared, less sensitive to air and moisture, and more economical. Therefore, we employed this reagent for optimization studies and scale-up with other lactones.

We took advantage of a number of modifications reported by Payack et al., including that in which $TiCp_2Me_2$ is prepared in situ as a toluene solution rather than isolating the solid reagent.[24] Although the concentration of this solution can be assayed, in practice this was

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(19) (a) Hudrlik, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1974**, *97*, 1464. (b) Hudrlik, P. F.; Peterson, D. *Tetrahedron Lett.* **1974**, 1133. (c) Utimoto, K.; Obayashi, M.; Nozaki, H. *J. Org. Chem.* **1976**, *41*, 2940.
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(21) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
(22) (a) Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212. (b) Tebbe, R. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.
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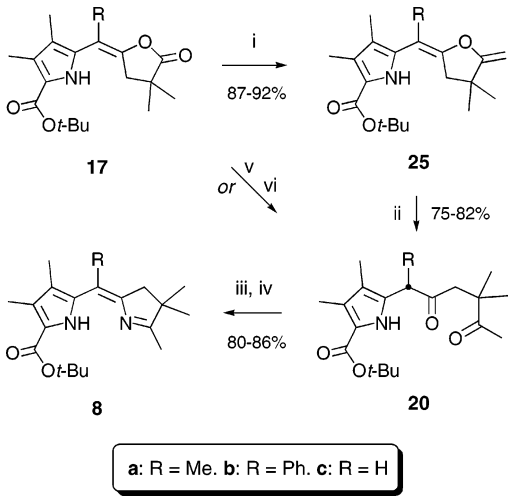
SCHEME 6[a]



[a] Reagents and conditions: i. $TiCp_2Cl_2$, MeLi, toluene, 0°C, 1 h, then **17**, cat. $TiCp_2Cl_2$, 80 °C, 6 h, then MeOH, H_2O, $NaHCO_3$, 40 °C, 14 h. ii. THF, 1 M HCl, room temperature, 1 h. iii. NH_3, THF, −33 °C to room temperature. iv. Montmorillonite K-10, THF, room temperature. v. Tebbe reagent, THF, −40 °C, then 1:1 TFA: H_2O, CH_2Cl_2, 80%. vi. $TiCp_2Me_2$, THF, 65 °C, then 1:1 TFA/H_2O, CH_2Cl_2, 61%.

generally not necessary. Even in excess the Petasis reagent is sufficiently selective that reaction can be prevented at other potentially labile sites in the molecule (vide infra). We also confirmed Payack's observation that small amounts of titanocene dichloride significantly reduced the reaction period, affording complete conversion after 6 h at 80 °C. Finally, the large volumes of petroleum ether or pentane required to precipitate titanium residues during workup were avoided by using Payack's improved isolation procedure, in which decomposition of residual titanium species was accomplished employing aqueous $NaHCO_3$/methanol. Following this protocol, we were able to obtain reproducible yields of enol ethers **25a**−**c** in the range of 87−92%. Alternatively, hydrolysis of the crude products in biphasic dichloromethane/aqueous TFA gave diketones **20a**−**c** in 75−82% overall yield.

In early experiments, we carried out the conversion of diketones **20a**−**c** to dihydrodipyrrins **8a**−**c** employing liquid ammonia followed by dehydration with Montmorillonite clay (Scheme 6, 80 − 86% yield). However, this method was less suitable for larger scale preparations and was often accompanied by decomposition. We also hoped to avoid the use of liquid ammonia. Utilizing diketone **20b**, we screened a large number of ammonia sources and solvent combinations to effect ring closure and subsequent dehydration. Of these, the combination of 14.8 N NH_4OH in DMF produced the best results and was also experimentally simple. Typically a solution of **20b** in DMF was stirred at room temperature with an excess of NH_4OH until initial hemiaminal formation was complete (6−8 h, TLC). The reaction was then acidified with 6 M HCl, which effected clean dehydration. This procedure routinely afforded 80−85% yields of *Z*-dihydrodipyrrin **8b** following chromatography.[16b] Moreover, we were able to streamline this synthesis to a very efficient "one-pot" transformation leading directly from enol ether **25b** to **8b**. In this modification **25b** was dissolved in DMF and treated with 1 M HCl, which effected rapid in situ hydrolysis to diketone **20b** with little or no decomposition (stronger acidic conditions, including 50% aqueous TFA, caused significant darkening). After hydrolysis was complete (TLC), the reaction mixture was treated with excess NH_4OH and allowed to continue stirring at room temperature. Finally, upon consumption of **20b** (TLC), the reaction was acidified to pH 1 with 6 M HCl to afford ∼85% of dihydrodipyrrin **8b** on gram scales (conditions A). Not surprisingly, a mixture of *E*/*Z*-isomers of **8b** is initially formed under these conditions. However, upon equilibration the *Z*-isomer is formed almost exclusively.[16b]

At this point we were disappointed to find that the conditions optimized for **25b** were not uniformly applicable. Despite repeated efforts, enol ether **17a** (R = Me) produced only trace amounts of dihydrodipyrrin **8a**, while enol ether **17c** (R = H) suffered extensive decomposition. These results are illustrative of a common phenomenon encountered in our study of these ring systems, in that closely related substrates can have markedly different reactivity profiles. In many cases, including **17a** and **17c**, these differences depend mainly upon the nature of the meso-substituent. For **17a**,**c**, our failure to effect amination probably reflects the sterically less-hindered (and more reactive) nature of intermediate diketones **20a**,**c**, which in NH_4OH undergo competing aldol reactions (cf. Schemes 4 and 6). Working from this premise, we were able to minimize side reactions with minor adjustments, substituting NH_4OAc/NEt_3 for the NH_4OH employed with **25b**. Under these conditions, decomposition was greatly reduced and *Z*-dihydrodipyrrins **8a**−**c** were obtained in 70−80% yield after warming at 55 °C (conditions B). In similar fashion, we synthesized dihydrodipyrrins **8d**,**e** utilizing the appropriate iodopyrroles **15** and alkyne acids **16** (Table 1).

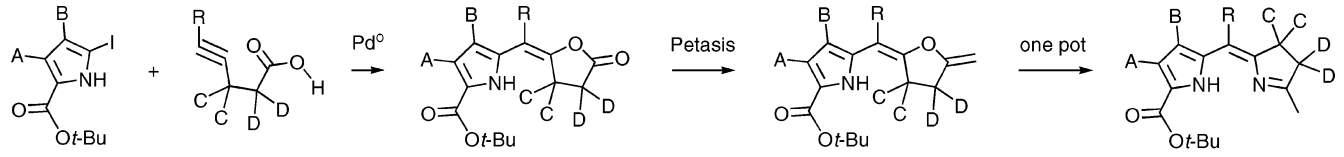
A diverse group of meso-groups R is accommodated by this methodology, ranging from H to Ar to *n*-alkyl. The most common side reaction observed in the Pd(0)-catalyzed reaction of iodopyrroles **15** and alkyne acids **16** was reduction of **15** to the corresponding α-unsubstituted pyrroles (i.e., I = H in **15**), which with $Pd[P(Ph)_3]_4$/$MeCN/NEt_3$ ranged up to 20%. However, C−I bond reduction was minimized by employing $Pd_2(dba)_3$ with two molecular equivalents of $P(Ph)_3$ or, alternatively, employing a large excess of K_2CO_3 in DMF with $Pd[P(Ph)_3]_4$. Mechanistic studies of this unusual Pd-promoted reductive deiodination, which if optimized could prove useful, are underway.[25]

Lipophilic substituents such as n-C_5H_{11} and n-$C_{10}H_{21}$ are of interest in designing more effective chromophores for PDT (vide supra), since they often have a favorable impact on partitioning of tetrapyrroles between normal and cancerous tissue,[5a] as well as on cell membrane penetration.[5b,c] The alkyne acids **16d** and **16e** required to introduce these substituents were readily prepared

(24) (a) Payack, J. F.; Hughes, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. *Organic Syntheses*; Wiley & Sons: New York, 2002; Collect. Vol. 79, p 19. (b) Payack, J. F.; Huffman, M. A.; Cai, D.; Hughes, D. L.; Collins, P. C.; Johnson, B. K.; Cottrell, I. F.; Tuma, L. D. *Org. Process Res. Dev.* **2004**, *8*, 256.

(25) For a similar observation, see: Leung, S. H.; Edington, D. G.; Griffith, T. E.; James, J. J. *Tetrahedron Lett.* **1999**, *40*, 7189.

TABLE 1. Isolated Yields for 17, 25, and 8a−i

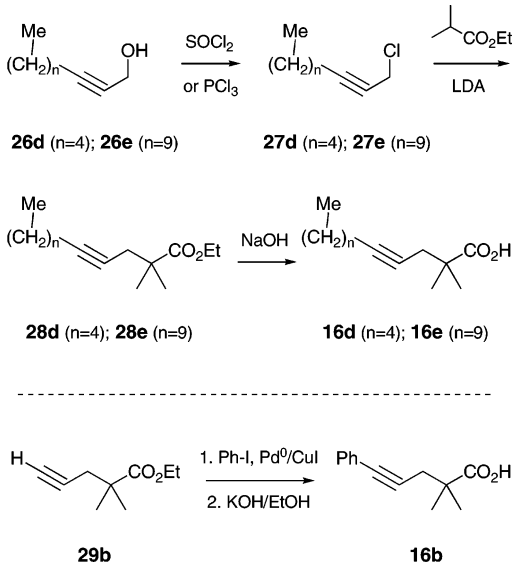


15 **16** **17** **25** **8**

	entry	substituents	yield **17** (%)	yield **25** (%)	yield[a] **8** (%)
group I	a	A,B,D = Me; C = H; R = Me	96	92	75[c]
	b	A,B,D = Me; C = H; R = Ph	85	87	85[b], 79[c]
	c	A,B,D = Me; C,R = H	98	87	71[c]
	d	A,B,D = Me; C = H; R = C_5H_{11}	77	76	60[c]
	e	A,B,D = Me; C = H; R = $C_{10}H_{21}$	69	75	66[c]
group II	f	A = $CH_2CH_2CO_2Me$ (= $\mathbf{P^{Me}}$); B,C = Me; D,R = H	73[e]	80	83[d]
	g	A,B,C = Me; D = H; R = H	74	86	65[c], 82[d]
group III	h	A,B = Me; C,D = H; R = H	68	72	53[c], 42[d]
	i	A,B = Me; C,D = H; R = Ph	71	55	45[c], 0[d]

[a] Yields refer to isolated and purified *Z*-**8** only and in most cases are not optimized. An additional 0−10% of **8** was obtained as the *E*-isomer. [b] Prepared according to conditions A. [c] Prepared according to conditions B. [d] Prepared according to conditions C. [e] Battersby et al. prepared the *Z*-isomer corresponding to lactone **17f** in 12 steps from 3,3-dimethylglutaric acid by a modification of the route described in Scheme 2.[14]

SCHEME 7



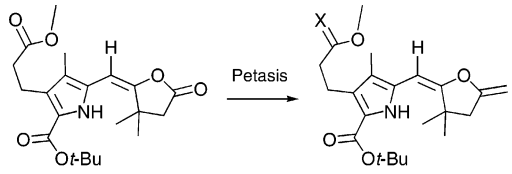
26d (n=4); **26e** (n=9) **27d** (n=4); **27e** (n=9)

28d (n=4); **28e** (n=9) **16d** (n=4); **16e** (n=9)

29b **16b**

from the commercially available propargyl alcohol derivatives **26d** and **26e**, following the sequence outlined in Scheme 7. Other alkyne acids were either commercially available (**16h**), known from the literature (**16a**, **16c**, **16g**, and **16i**)[26,29b] or produced in straightforward fashion. For example, **16b** (R = Ph) was prepared in high yield by Sonogashira coupling of iodobenzene with the known alkyne ester **29b**,[26a] followed by base hydrolysis.

SCHEME 8



17f **25f** (X=O) (69%)
30 (X=CH_2)

Enelactones **17a−e** differ only in the meso-substituent R, having A, B, D = Me and C = H (cf. Table 1). However, **17f** contains a propionate ester (P^{Me}) that might undergo competitive Petasis reaction (Scheme 8). In practice, this group presented few complications so long as reaction was stopped immediately upon consumption of starting lactone **17f** (TLC). Prolonged reaction times led to the formation of the corresponding bis-enol ether derivative **30**. However, even this side reaction might be eliminated employing a "sacrificial" ester as very recently described by Payack et al.[24b]

In all cases where D = methyl the transformation of diketones **20** to **8** was reliable, employing our standard reaction conditions (NH_4OAc/NEt_3/DMF/55 °C, conditions B), and afforded good overall yields of dihydrodipyrrins **8** (Table 1). With other regioisomers, however, it was necessary to devise modified reaction conditions to avoid side reactions. For example, the diketones **20f** and **20g** (D = H) were prone to competitive aldol condensation and afforded significant quantities of byproducts **22f** and **22g** (Scheme 9). We attribute this change in reactivity pattern to the fact that the initial aldol products **31f**,**g** are relatively strain-free, containing no adjacent quaternary centers. In contrast, the regioisomeric diketone **20c** is much less reactive toward aldol condensation to give **32c**, which introduces significant steric strain. The only exception thus far observed to this pattern is with the silicon-substituted diketone **21c** (cf. Scheme 4), which we believe represents a special case. Also of interest, the alternative aldol pathway involving nucleophilic participation of the methyl ketone is operative only under

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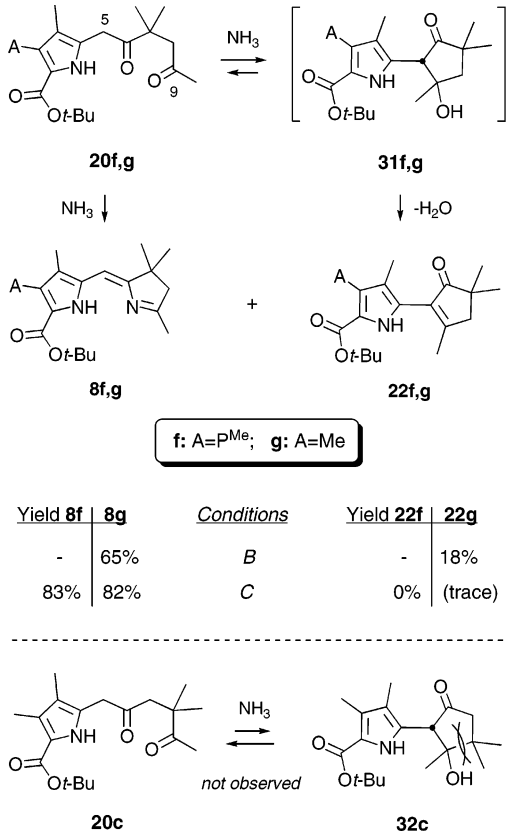
(27) O'Neal, W. G.; Roberts, W. P.; Ghosh, I.; Jacobi, P. A. Studies in Chlorin Chemistry. III. A Scalable Synthesis of Chlorins. Manuscript in preparation.

(28) Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Am. Chem. Soc.* **1984**, *106*, 5594.

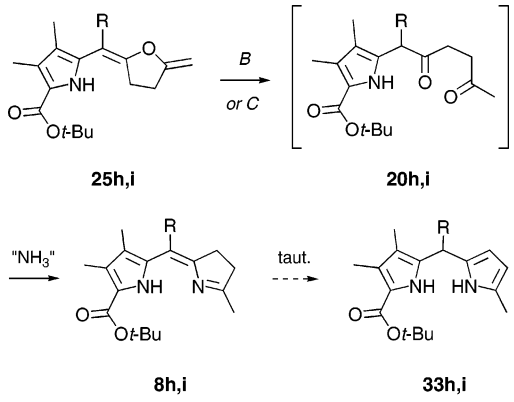
(29) (a) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749. (b) Jacobi, P. A.; Pippin, D. *Org. Lett.* **2001**, *3*, 827 and references therein.

SCHEME 9



Yield 8f	8g	Conditions	Yield 22f	22g
-	65%	*B*	-	18%
83%	82%	*C*	0%	(trace)

SCHEME 10



Yield 8h	8i	Conditions	Yield 33h	33i
0%	0%	*B (55 °C)*	59%	71%
53%	45%	*B (25 °C)*	< 2%	10%
42%	0%	*C*	(trace)	0%

special circumstances.[27] In the event, we eventually found that both categories of aldol reaction are largely circumvented by effecting the aminolysis of diketones **20f**,**g** at 0 °C with NH_4OAc in DMF, omitting added NEt_3. Even better results were achieved employing the more soluble (and anhydrous) ammonium propionate ($NH_4^+EtCO_2^-$),[28] which afforded 80−85% yields of **8f**,**g** after 18 h in DMF at 0 °C (conditions C).

A complication of a different nature was encountered with enol ethers **25h** and **25i**, where the initially formed dihydrodipyrrins **8h**,**i** underwent facile aromatization to the dipyrromethanes **33h**,**i** (Scheme 10). In our first experiments enol ethers **25h**,**i** were dissolved in DMF and hydrolyzed in situ with 1 M HCl as described previously. After diketone formation was complete (TLC) the reaction mixture was treated with excess NH_4OAc/NEt_3 and heated to 55 °C (conditions B). Under these conditions, the sole identifiable products were dipyrromethanes **33h** (59%) and **33i** (71%), respectively. In the case of enol ether **25h** aromatization was effectively eliminated by carrying out aminolysis at ambient temperature and limiting reaction time to 4 h. Longer reaction times led to increasing formation of **33h** even at room temperature. Using the same reagents, we found that enol ether **25i** afforded 45% of dihydrodipyrrin **8i** together with 10% **33i**, but the final aminolysis was much slower (∼48 h). To better understand these transformations, diketones **20h**,**i** were isolated and subjected to a variety of cyclization conditions. Diketone **20h** proved to be significantly more reactive toward aminolysis with NH_4OAc in DMF, even in the absence of NEt_3. However, no particular benefit was realized with this modification, which still afforded small amounts of dipyrromethane **33h** at temperatures down to 0 °C. Moreover, starting material was still present after 72 h. Similar results were realized with $NH_4^+EtCO_2^-$ in DMF (conditions C), which while experimentally more convenient afforded no improvement in rate or selectivity relative to NH_4OAc. After 24 h at 0 °C, **20h** gave a 42% yield of dihydrodipyrrin **8h** together with trace amounts of **33h**. In contrast, diketone **20i** proved to be essentially unreactive at 0 °C, with little **8i** evident after one week. On the basis of these experiments, the most convenient route to dihydropyrrins **8h**,**i** remains the simple modification to conditions B described above, where aminolysis is carried out at room temperature (cf. Scheme 10). In any event, complications of this type will be rare since in most cases aromatization is blocked by geminal alkyl substituents.

Thus far we have identified three structural categories of enol ethers **25** (groups I−III, Table 1), each of which has distinct reactivity patterns that must be taken into account for efficient conversion to **8**. For clarity, we summarize in Figure 3 our optimized conditions for the one-pot conversion of each of these variants of **25** to dihydrodipyrrins **8**. Enol ethers of group I are perhaps the most straightforward, since the geminal Me-substituents at C-8 effectively block competing aldol reactions (cf. bottom of Scheme 9). Of these, enol ether **25b** (R = Ph) is a particularly favorable substrate and is converted to dihydrodipyrrin **8b** in excellent overall yield employing conditions A. The remaining members of this group are somewhat more prone to side reactions and require a buffered medium for aminolysis (conditions B; NH_4OAc/NEt_3 replaces NH_4OH; 25−55 °C). Enol ethers of group II have geminal Me-substituents at C-7, and their hydrolysis products **20** undergo competitive aldol condensation linking C-5 and C-9 (cf. Scheme 9). This side reaction is effectively eliminated by carrying out aminolysis under conditions C, which in particular avoids basic conditions (NH_4OAc or $NH_4^+EtCO_2^-$/DMF/0 °C; no NEt_3). Given that most naturally occurring hydroporphyrins have geminal substituents at C-7, conditions C may prove to be most useful for the preparation of dihydrodipyrrin precursors

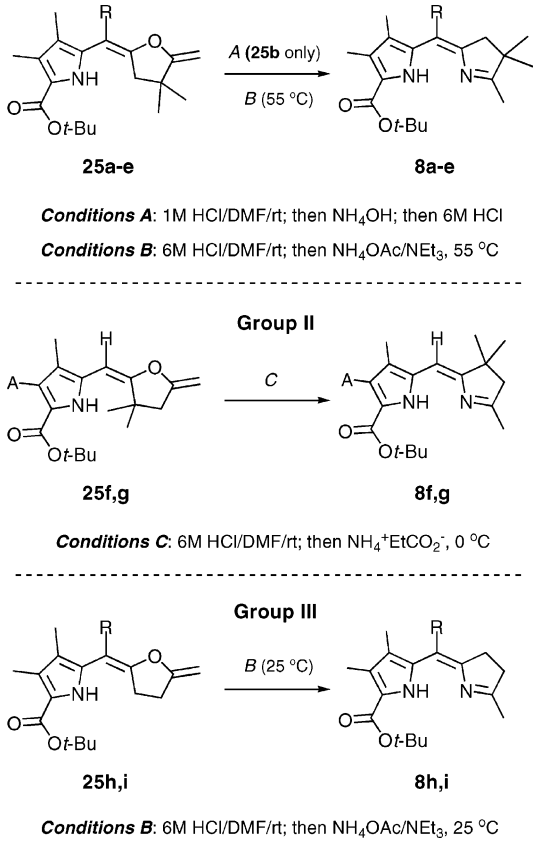
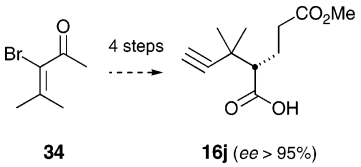


FIGURE 3. Summary of conditions A−C.

SCHEME 11



of such compounds. The last category of enol ethers **25** consists of the unsubstituted members of group III, whose amination products **8h**,**i** are susceptible to aromatization. Although conditions C partly mitigate this problem, the most convenient means of avoiding aromatization is by employing conditions B at 25 °C.

Finally, this methodology should be readily adaptable to the synthesis of homochiral dihydrodipyrrins **8**, limited only by the availability of the requisite chiral alkyne acids **16**. For this purpose, we are developing efficient protocols for synthesizing these substrates, utilizing either a Nicholas−Schreiber reaction[29] or a variant of Ireland's enantioselective ester-enolate Claisen rearrangement.[30a] For example, in companion studies we recently described the enantioselective synthesis of alkyne acid **16j** (ee > 95%),[30b] which we are employing as a ring-C synthon in our work on cobyric acid (Scheme 11). Alkyne acid **16j** also has the proper substitution pattern for preparing the A,B-ring portion of bonellin (**2**). Enantioselective syntheses of **2** and other naturally occurring hydroporphyrins are currently in progress.

Experimental Section

Representative Procedure for Syntheses of Dihydrodipyrrins 8. Dihydrodipyrrin 8b: 5-[(4,4-Dimethyl-5-oxo-dihydro-furan-2-ylidene)-phenyl-methyl]-3,4-dimethyl-1*H*-pyrrole-2-carboxylic Acid *tert*-Butyl Ester (17b).[16] A solution of 4.00 g (12.5 mmol) of iodopyrrole **15a**, 3.70 g (18.3 mmol) of alkyne acid **16b**, and 4.46 g (14.0 mmol) of $BnNEt_3Cl$ in 146 mL of CH_3CN and 29 mL NEt_3 was purged with argon for 10 min and then treated with 1.42 g (1.1 mmol) of $Pd(PPh_3)_4$. The resulting solution was flushed with argon and heated at reflux for 17 h. At the end of this period, the reaction was concentrated to dryness under reduced pressure and the residue was partitioned between CH_2Cl_2 and water. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:20) to give 4.2 g (85%) of lactone **17b** as a colorless crystalline solid, mp 129 °C; R_f (1:5 EtOAc/hexanes) 0.60; IR (thin film) 3289, 3056, 1800, 1672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 6H), 1.60 (s, 9H), 1.91 (s, 3H), 2.33 (s, 3H), 2.72 (s, 2H), 7.31−7.39 (m, 5H), 8.59 (bs, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 9.7, 11.0, 25.0, 28.7, 39.7, 41.8, 80.9, 109.8, 119.9, 120.5, 126.1, 127.3, 128.4 (2C), 128.8 (2C), 128.9, 135.9, 147.2, 161.6, 179.9; Anal. Calcd. for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.71; H, 7.43; N, 3.55.

5-[(4,4-Dimethyl-5-methylene-dihydro-furan-2-ylidene)-phenyl-methyl]-3,4-dimethyl-1*H*-pyrrole-2-carboxylic Acid *tert*-Butyl Ester (25b). A suspension of 1.47 g (5.97 mmol) of titanocene dichloride in 16 mL of anhydrous toluene was treated with 8.2 mL (13.1 mmol) of 1.6 M methyllithium in diethyl ether over 5 min at 0 °C. After stirring the solution for 1 h at 0 °C, we quenched the reaction with 14 mL of 6% NH_4Cl. The organic layer was separated and washed sequentially with water and brine. It was then dried over Na_2SO_4 and filtered to give an orange solution of dimethyl titanocene. This solution was treated with 0.502 g (1.26 mmol) of lactone **17b** and 19 mg (0.076 mmol) of titanocene dichloride and heated in the dark at 80 °C for 6 h. At the end of this period, the flask was cooled to room temperature and 1.5 mL of methanol, 63 mg of $NaHCO_3$, and 15 μL of water were added. The solution was stirred for 12 h at 40 °C. The resulting green solution was filtered through a pad of Celite, which was further washed with hexanes. If necessary, the filtrate was filtered a second time, and the solvents were then removed under reduced pressure. The resulting oil was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:10 with 1% NEt_3) to give 0.43 g (87%) of enol ether **25b** as a colorless crystalline solid, mp 146−147 °C. R_f (1:4 EtOAc/hexanes) 0.51; IR (thin film) 3303, 2970, 1660, 1240, 1129 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 6H), 1.57 (s, 9H), 1.85 (s, 3H), 2.29 (s, 3H), 2.45 (s, 2H), 4.08 (d, J = 2.44, 1H), 4.51 (d, J = 2.44, 1H), 7.30 (m, 5H), 8.35 (br s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 9.8, 11.1, 27.5, 28.8, 39.5, 44.3, 80.6, 82.0, 104.1, 119.7, 126.2, 126.3, 128.3, 128.5, 131.1, 137.4, 154.1, 161.6, 170.5 (one overlapping aromatic signal). Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56; O, 12.20. Found: C, 76.25; H, 7.98; N, 3.59.

3,4-Dimethyl-5-[phenyl-(4,4,5-trimethyl-3,4-dihydro-pyrrol-2-ylidene)-methyl]-1*H*-pyrrole-2-carboxylic Acid *tert*-Butyl Ester (8b). Conditions A. A solution of 0.95 g (2.41 mmol) of **25b** in 23 mL of DMF was treated with 1.2 mL (1.21 mmol) of 1 M HCl and stirred at room temperature until TLC indicated complete formation of the intermediate diketone [~1 h; R_f (1:4 EtOAc/hexanes) 0.22]. The solution was then treated with 3.3 mL (48.2 mmol) of 14.8 M NH_4OH and stirred at room temperature until TLC indicated complete consumption of the diketone (~6 h). 6 M HCl (7.2 mL; 43.4 mmol) was then added until a pH of 1 was achieved, and the solution was

(30) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Varney, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 3668. (c) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650. (d) Koch, G.; Janser, P.; Kottirsch, G.; Romero-Giron, E. *Tetrahedron Lett.* **2002**, *43*, 4837 and references therein. (e) Jacobi, P. A.; Tassa, C. *Org. Lett.* **2003**, *5*, 4879.

stirred for a further 14 h at room temperature. The resulting solution was poured into cold, saturated $KHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed sequentially with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:4 to 1:1) to give 0.81 g (86%) of imine **8b** as a crystalline solid, mp 184−185 °C. R_f (1:4 EtOAc/hexanes) 0.47; IR (thin film) 3286 (br), 1692, 1429, 1173 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 6H), 1.21 (s, 3H), 1.61 (s, 9H), 2.18 (s, 3H), 2.20 (s, 3H), 2.36 (s, 2H), 7.26 (m, 5H), 11.59 (br s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 10.2, 10.4, 16.0, 25.9, 28.75, 28.78, 44.6, 48.2, 79.8, 119.5, 119.8, 120.9, 127.2, 128.7, 129.9, 130.9, 140.2, 150.5, 161.3, 187.7. Anal. Calcd for $C_{25}H_{32}N_2O_2$: C, 76.49; H, 8.22; N, 7.14; O, 8.15. Found: C, 76.56; H, 8.59; N, 6.78.

Conditions B. A solution of 0.102 g (0.25 mmol) of enol ether **25b** in 2.4 mL of DMF was treated with 21 μL (0.13 mmol) of 6 M HCl and stirred until formation of the diketone was complete by TLC [~1 h; R_f (1:4 EtOAc/hexanes) 0.22]. The reaction was then treated with 0.40 g (5.1 mmol) of NH_4OAc and 0.70 mL (5.1 mmol) of NEt_3. The resulting solution was heated at 55 °C until product formation was complete by TLC [~6 h; R_f (1:4 EtOAc/hexanes) 0.47]. The reaction was then diluted with 10% KH_2PO_4 (2.4 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed sequentially with water (2 × 10 mL) and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:9) to give 0.079 g (79%) of imine **8b** as a crystalline solid that was identical in all respects to the compound prepared using conditions A described in the previous paragraph.

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Supporting Information Available: Experimental details, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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