Tetrahedron 66 (2010) 4413–4422

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Porphyrins with exocyclic rings. Part 25: synthesis of porphyrins with a fused cyclic ether subunit from tetrahydro-4*H*-pyan-4-one☆

Breland E. Smith, Timothy D. Lash *

Department of Chemistry, Illinois State University, Normal, IL 61790-4160, USA

ARTICLE INFO

Article history:
Received 23 February 2010
Received in revised form 15 April 2010
Accepted 16 April 2010
Available online 21 April 2010

Keywords:
Porphyrins
Crown ethers
Conformational analysis
Knorr pyrrole Synthesis
MacDonald condensation

ABSTRACT

A novel porphyrin system with a fused dihydropyran ring has been synthesized from commercially available 4-oxotetrahydropyran. The cyclic ketone reacted with oximes derived from acetoacetate esters in the presence of zinc dust, sodium propionate, and propionic acid at 150–155 °C to give good yields of 5-oxatetrahydroindoles. A low yield of a benzo-fused analog was also obtained using 4-oxochromanone as the starting reagent. Reaction of the *b*-annelated pyrroles with *N*-chlorosuccinimide gave the 7-chloro-derivatives and these underwent an acid catalyzed condensation with α-unsubstituted pyrroles to give dipyrrolic products linked by a dihydropyran moiety. Hydrogenolysis of a dipyrrole dibenzyl ester gave the corresponding dicarboxylic acid and this was converted into a dialdehyde by treatment with TFA–$CH(OMe)_3$. MacDonald '2+2' condensation with two different dipyrrylmethanes under optimized conditions afforded the porphyrin ethers in 30–36% yield. This approach provides a pilot study for the synthesis of porphyrin crown ether structures. In addition, insightful results on the conformations of dihydropyran-linked dipyrroles were obtained by careful examination of their proton NMR spectra in $CDCl_3$ and DMSO-d_6.

1. Introduction

Porphyrins with fused carbocyclic rings are widely found in petroleum, oil shales, and other organic-rich sedimentary materials.[1,2] Cycloalkanoporphyrins **1** with fused five-, six- or seven-membered rings have been identified and these geoporphyrins provide insights into the origins of fossil fuels.[3,4] These porphyrins are commonly present in metalated forms, usually as the nickel(II) or vanadyl derivatives, and in most cases appear to be derived from the chlorophylls that were associated with organisms (mostly algae or photosynthetic bacteria) that were present at the time these sediments were initially laid down.[1,2] Analytical methods have been developed to examine and contrast the porphyrins present in sedimentary materials[5] and these can potentially lead to applications in environmental monitoring, specifically in the analysis of tar balls resulting from oil spills.[6–8] In order to provide reliable standards for these investigations, synthetic methods have been developed for the synthesis CAPs with 5-, 6-, 7- or larger exocyclic rings.[9–17] We have previously reported on the synthesis of CAPs from cycloalka[*b*]pyrroles **2**, which in turn could be obtained from readily available cyclic ketones.[13–17] For instance, cyclohexanone in acetic acid reacted with phenylhydrazones **3**, or the related oximes, in the presence of zinc powder to give tetrahydroindoles **4** (Scheme 2),[16] and similar cycloalka[*b*]pyrroles can be obtained by application of the same Knorr-type chemistry.[13–18] Tetrahydroindoles **4** were regioselectively oxidized with lead tetraacetate to afford the 7-acetoxy derivatives **5** and these in turn could be reacted with α-unsubstituted pyrroles **6** in the presence of *p*-toluenesulfonic acid to give dipyrroles **7**.[16] Deprotection of the ester moieties and further reaction (e.g., with dipyrrylmethane dialdehydes) gave *meso*, β-propanoporphyrins **8** (CAP6) in good overall yields (Scheme 2).[16] The same approach can be applied to the synthesis of CAPs with virtually any size exocyclic ring component.[13–17] The six-membered ring intermediates were particularly versatile and have allowed the straightforward synthesis of porphyrins **9** with four exocyclic rings (Scheme 3).[15a] To date, this synthetic methodology had only been applied to the preparation of porphyrins with fused carbocyclic rings, but in principle the same concepts could be applied to the synthesis of porphyrins with fused heterocyclic systems.

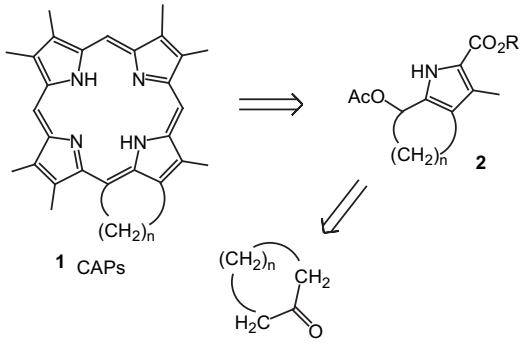
Porphyrins with appended crown ethers have been widely investigated and have properties that are desirable for sensor development and molecular recognition studies.[19] Naturally, the porphyrin macrocycle retains the ability to form coordination complexes while the crown ether units can also strongly bind with alkaline metal cations.[19–21] However, few examples of porphyrins with fused crown ether units have been reported.[21] Murashima et al. reported an interesting series of porphyrin fused crown ethers

☆ For part 24 in the series, see: Gandhi, V.; Thompson, M. L.; Lash, T. D. *Tetrahedron* **2010**, *66*, 1787–1799.

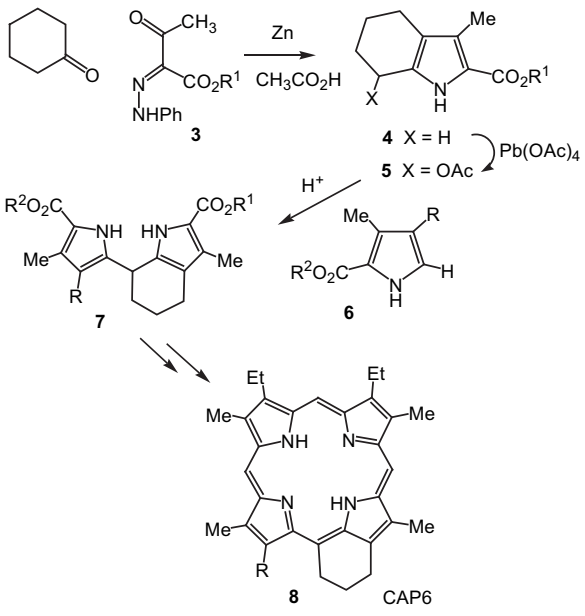
* Corresponding author. Fax: +309 438 5538; e-mail address: tdlash@ilstu.edu (T.D. Lash).

0040-4020/$ – see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tet.2010.04.069

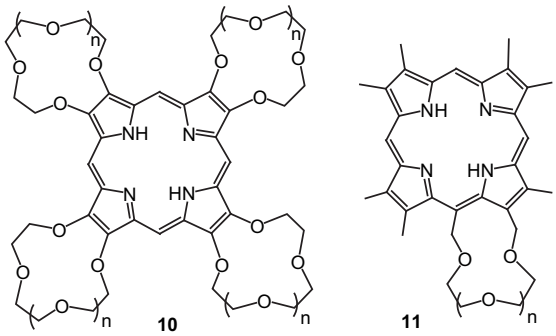
10 where the oxygens are directly connected to the β-pyrrolic carbons.[21] We speculated that crown ether analogs of CAPs **1** would also have useful properties. Specifically, porphyrin crown ethers **11** might induce a sufficiently large conformational change on binding metal cations that they would distort the porphyrin macrocycle and thereby provide a potential avenue for detector development based on changes in the visible absorption spectrum or in fluorescence emission intensity. Therefore, we set out to explore the synthesis of porphyrins with a fused ether subunit as a model for the development of structures like **11**. It was anticipated that the strategies we had previously developed for synthesizing CAPs **1** could be adapted to prepare these porphyrin ethers. In this paper, we report the synthesis of porphyrins with a fused dihydropyran moieties using this approach (Scheme 1).[22]

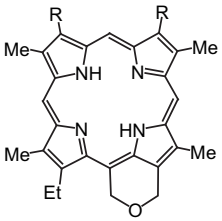


Scheme 1.



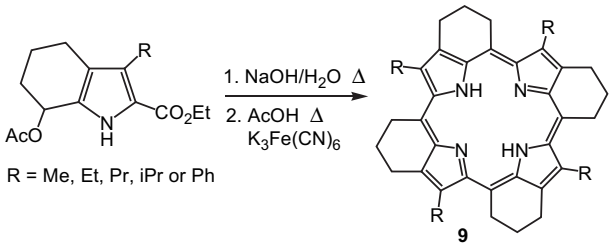
Scheme 2.



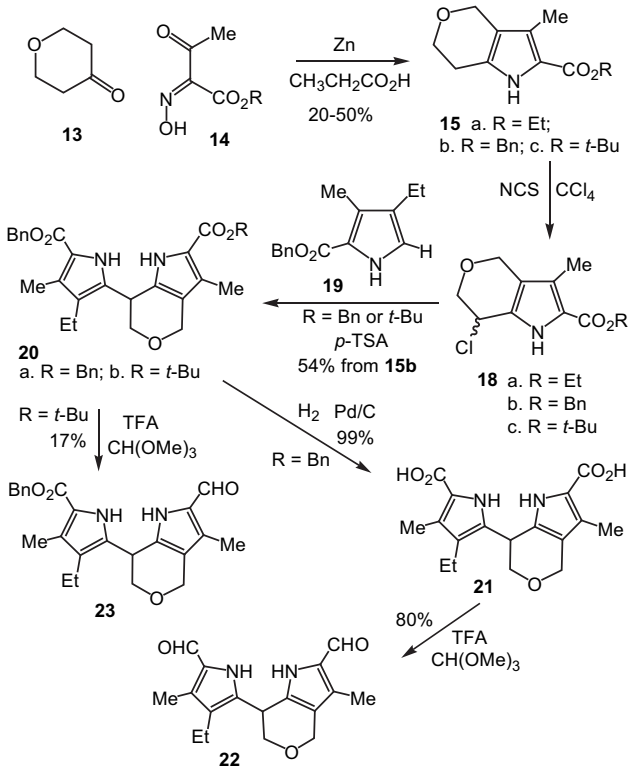


2. Results and discussion

In this study, *meso*,β-(2-oxapropano)porphyrins **12** (R=Et or $CH_2CH_2CO_2Me$) were targeted for investigation. This system is the dihydropyran analog of cycloalkanoporphyrins **8**, which were ultimately synthesized from cyclohexanone. Therefore, it was anticipated that the porphyrin ether system could be obtained starting from tetrahydropyran-4-one **13**. In the earlier studies, tetrahydroindoles **4** were prepared using classical Knorr-type conditions by reacting phenylhydrazones **3** with cyclohexanone and zinc dust in acetic acid at 110 °C.[15,16,18,23] In most Knorr-type reactions, oximes are used instead of phenylhydrazones but better results were generally obtained for cyclic ketones using phenylhydrazones.[15–17] Most Knorr reactions are also conducted at lower temperatures (70–80 °C) and yields plummet if the temperature of the exothermic reaction goes too high. However, much higher temperatures are necessary for the synthesis of many cycloalka[*b*]pyrroles and in the case of larger rings virtually no product is obtained unless the reaction temperature is raised to >140 °C.[17] In those reactions, propionic acid was substituted for acetic acid as the reaction solvent. Reactions with cyclopentanone necessitated temperatures >150 °C,[14b] and these temperatures were obtained by dissolving substantial amount of sodium propionate in the reaction solvent. Reactions with **13** were attempted using oximes **14**[14b] or phenylhydrazones **3**[15a] in acetic acid under the conditions used to prepare tetrahydroindoles **4**, but very low yields of the desired dihydropyranopyrrole or 5-oxotetrahydroindole product **15** were obtained (Scheme 4). Following a series of attempts, the best results were obtained using oximes **14** at reaction temperatures of 150–155 °C in mixtures of sodium propionate and propionic acid. The chemistry was accomplished by heating a stirred mixture of **13**, sodium propionate, and propionic acid to 150 °C and then adding a solution of the oxime **14** in propionic acid while simultaneously adding small portions of zinc dust over a period of ca. 30 min. After the addition was completed, the mixture was stirred for a further 1 h. These conditions gave good yields for ethyl ester **15a** and benzyl ester **15b**, but poor results were still obtained for the related *tert*-butyl ester **15c**. However, we observed that reactions with oxime **14c** darkened considerably when they were heated for 1 h after the addition of the reactants had been completed. As it was unclear how long the reaction mixture needed to be heated, the reaction time following the addition was reduced to 5 min and the reaction mixture was rapidly quenched by pouring it into ice-water. This modification raised the yield of **15c** to 20%; however, reducing the reaction time for esters **15a** and **15b** had little or no effect on the observed yields. Dihydropyrano[3,4-*b*]pyrroles **15** are novel

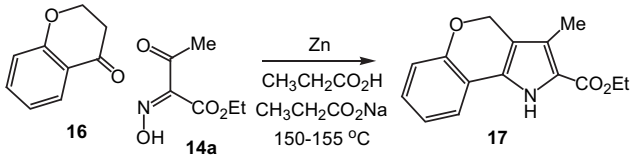


Scheme 3.



Scheme 4.

heterocyclic compounds and are obtained in a very simple fashion using the Knorr approach. In fact, this is the first time that Knorr-type chemistry has been used to prepare pyrroles with fused heterocyclic rings. Therefore, we speculated that other heterocyclic systems could be obtained using the same methodology. With this in mind, 4-chromanone (**16**) was reacted with oxime **14a** and zinc dust in an attempt to prepare the pyrrolic tricycle **17** (Scheme 5). Again, the best results were obtained at 150–155 °C in mixtures of sodium propionate and propionic acid, but in this case yields of **17** were relatively low (ca. 6%). Although this chemistry allows for a remarkably direct synthesis of this novel chromanopyrrole system, it is clearly not practical. As the structure of **17** is not compatible with porphyrin synthesis, this tricyclic system was not further investigated.



Scheme 5.

In order to utilize dihydropyrano[3,4-*b*]pyrroles **15**, it was necessary to introduce a leaving group on the α-methylene unit. Tetrahydroindoles **4** react with lead tetraacetate in acetic acid to give the related acetoxy compounds **5** (Scheme 2),[15,16] but the dihydropyranopyrroles gave no isolatable products with this reagent. Instead, **15a** and **15b** were reacted with *N*-chlorosuccinimide (NCS) in carbon tetrachloride in the presence of a strong lamp (Scheme 4). The chemistry was somewhat sluggish, taking several hours to reach completion, but the reaction could easily be monitored by proton NMR spectroscopy. The resulting chloro-derivatives **18** were somewhat unstable and were taken on in crude form. Tetrahydroindoles had been used to prepare porphyrins **9** with four exocyclic rings (Scheme 3),[15a] and this chemistry was also investigated using ethyl ester **18a** in an attempt to prepare the tetraoxa-analog of these unusual porphyrins. The ester was saponified in refluxing sodium hydroxide, and the crude product was treated with potassium ferricyanide in refluxing acetic acid. Unfortunately, this procedure afforded no trace of porphyrin products and attempts to prepare symmetrical porphyrin ethers were abandoned. The failure of this chemistry was attributed to the poor stability of the intermediates and the reduced reactivity of the bicyclic pyrrolic unit caused by the presence of a nearby electronegative oxygen atom.

Benzyl ester **18b** was reacted with an α-unsubstituted pyrrole **19** in acetic acid, using *p*-toluenesulfonic acid as a catalyst, and this afforded a dipyrrole **20a** that was linked via the dihydropyran unit (Scheme 4). The benzyl ester protective groups were cleaved by hydrogenolysis over 10% Pd/C to give the corresponding dicarboxylic acid **21** in quantitative yield. The dicarboxylic acid could be isolated in pure form, but had to be handled with care or partial decomposition ensued. The related dialdehyde **22** was also required and this was generated by treating **21** with TFA and then adding trimethyl orthoformate while maintaining the temperature at 25 °C, followed by stirring the reaction for 10 min at 40 °C. The outcome of this reaction was somewhat sensitive and higher or lower temperatures gave poor results. In our studies, we commonly isolate dipyrrole dicarboxylic acids by carefully precipitating the products from an aqueous ammonia solution by acidification with acetic acid at 5 °C, followed by suction filtration, exhaustive washing with water, and drying in vacuo.[16,17] However, material obtained this way gave variable results and better results were generally obtained when the dicarboxylic acid was taken on with a minimum of handling following the hydrogenolysis step. The synthesis of a dipyrrole **20b** with mixed ester units was also investigated. Pyrrole **15c** was reacted with NCS in carbon tetrachloride but gave relatively poor results. Although the chloro-derivative **18c** was generated, the reaction had to be stopped before going to completion to avoid decomposition. The product was then reacted with **19** and *p*-toluenesulfonic acid in acetic acid to form the required dipyrrole. This compound was isolated following column chromatography as an oil and used directly to generate a dipyrrole aldehyde **23**. The oil was stirred with TFA at room temperature for 10 min and treated with trimethyl orthoformate. Following chromatography and recrystallization, aldehyde **23** was obtained in 17% yield. The chemistry observed for dihydropyranopyrroles is significantly modified by the 5-oxa substitution compared to tetrahydroindoles. The oxygen appears to exert enough of an electron-withdrawing effect to reduce the reactivity of the 7-position towards reactions with lead tetraacetate or NCS. In addition, it is far less straightforward to convert dipyrrolic intermediates in the dihydropyran series into the corresponding aldehydes. Nevertheless, dipyrroles **20a**, **21**, and **22** could all be isolated in good to excellent yields under optimized conditions.

The NMR properties for dihydropyranopyrroles **15**, and the solvent dependent results for dipyrroles **20a** and **22**, were sufficiently unusual to warrant further discussion. In the monopyrroles (e.g., **15a**; Fig. 1), the isolated 4-CH_2 group gave a downfield signal at 4.6 ppm, while the resonances for the 6- and 7-methylene units showed up at 3.9 and 2.7 ppm, respectively. Although these shifts are to be expected, the 4-CH_2 unit gave a broadened long range coupled triplet (J=1.2 Hz), while the 7-CH_2 gave a broadened triplet that showed indications of long range coupling as well. This degree of $^5J_{HH}$ coupling interaction across the pyrrolic unit is somewhat unexpected and is analogous to homoallylic coupling in olefinic systems. The interaction was confirmed using $^1H-^1H$ COSY NMR spectroscopy. Long range coupling of this type was weak in dipyrroles **20**–**22**, and while the interactions gave rise to some peak broadening, only weak correlations could be seen by COSY NMR spectroscopy. However, the proton NMR data for the dipyrroles provides some important information on the conformations of

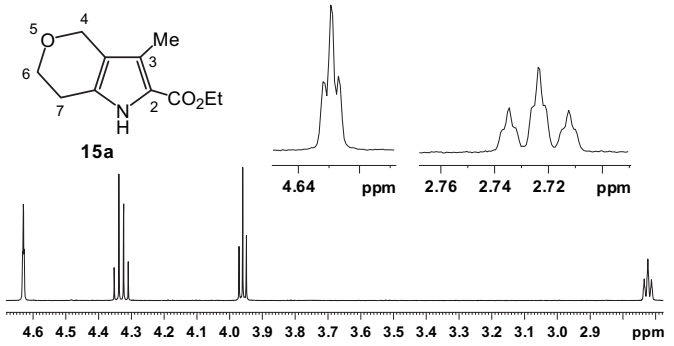


Figure 1. Partial 500 MHz proton NMR spectrum of 5-oxatetrahydroindole **15a** in $CDCl_3$ showing the unusual ^5J coupling between the 4- and 7-CH_2 protons at 2.72 and 4.63 ppm, respectively.

these intermediates. At 500 MHz, the three protons at positions 6 and 7 on the dihydropyran unit of **20a** are sufficiently well resolved to represent an AMX system (Fig. 2). In addition, the protons corresponding to the 4-CH_2 moiety gave an AB quartet (J=13.5 Hz) at 4.7 ppm. The ethyl CH_2 was also diastereotopic and gave rise to a multiplet centered on 2.47 ppm. In DMSO-d_6, significant changes were observed in these proton NMR resonances (Fig. 3). The peaks

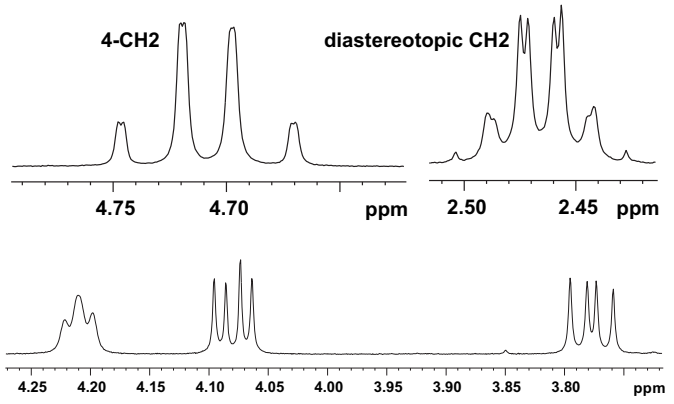


Figure 2. Partial 500 MHz proton NMR spectrum of dipyrrole **20a** in $CDCl_3$ showing an AB quartet at 4.7 ppm for the 4-CH_2 and a multiplet for the diastereotopic ethyl CH_2 at 2.43–2.51 ppm. The AB quartet is slightly broadened due to long range coupling effects. The region between 3.70 and 4.25 ppm corresponds to the $CHCH_2$ unit of the dihydropyran ring and the J values for this system are consistent with conformation A.

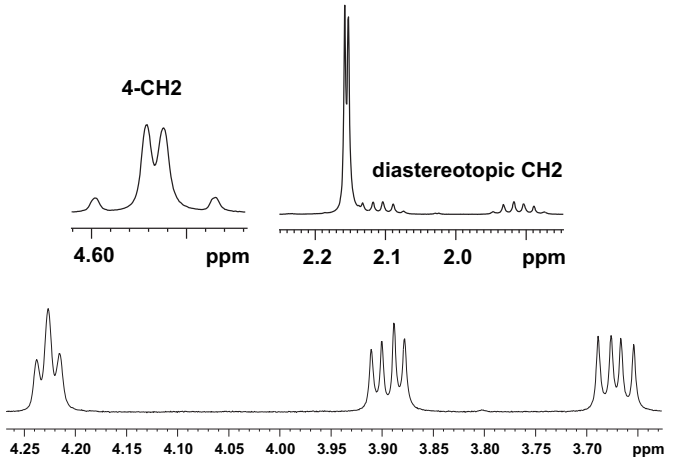


Figure 3. Partial 500 MHz proton NMR spectrum of dipyrrole **20a** in DMSO-d_6 showing an AB quartet at 4.5 ppm for the 4-CH_2 and two well resolved 1H multiplets for the diastereotopic ethyl CH_2 at 1.9 and 2.1 ppm. The region between 3.65 and 4.25 ppm corresponds to the $CHCH_2$ unit of the dihydropyran ring and the J values for this system are again consistent with conformation A.

corresponding to the 4- and 6-methylenes were shifted upfield by 0.1–0.2 ppm, while the ethyl CH_2 gave rise to two widely separated multiplets at 1.9 and 2.1 ppm (Fig. 3). The upfield shift and increased resolution of this diastereotopic methylene indicates that the ethyl group is held under the π-system of the adjacent pyrrole unit, and this geometry presumably results from favorable hydrogen bonding interactions with the DMSO solvent (Fig. 4). The upfield shift of the ethyl CH_3 resonance from 1.10 ppm in $CDCl_3$ to 0.77 ppm in DMSO-d_6 also supports this conjecture. Nevertheless,

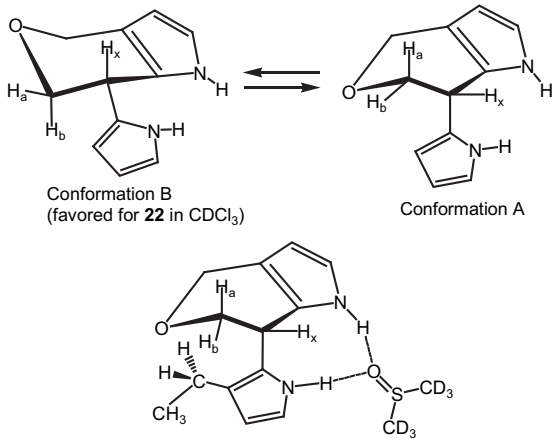


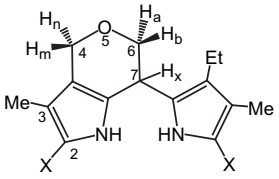
Figure 4. Proposed equilibrium of conformations A and B for dihydropyran-linked dipyrroles. Substituents are not shown for the sake of clarity. Hydrogen bonding to DMSO favors a type A conformation but holds the ethyl substituent in a specific orientation relative to the adjacent pyrrole ring.

the ^3J coupling constants for the two protons at position 6 and the adjacent 7-CH fell into the range of 5.0 to 7.1 Hz in both solvents (Table 1), values that are consistent with the 60° dihedral angles in conformation A (Fig. 4). The proton NMR spectrum for dialdehyde **22** in DMSO-d_6 showed similar coupling interactions for the $CHCH_2$ unit with vicinal coupling constants of 5.3 and 6.8 Hz, values that again suggest that conformation A is favored, and the ethyl CH_2 also shows an upfield shift and strongly diastereotopic characteristics. However, the proton NMR spectrum of **22** in $CDCl_3$ showed significant differences in the coupling for the CH_2CH unit. In this case, the 6-CH_2 resonances are significantly shifted upfield and show vicinal coupling constants with the 7-CH of 5.7 and 9.5 Hz (Table 1). This coupling interaction is not consistent with conformation A and suggests that the alternative conformation B is more favored in this case (Fig. 4). Conformation B has dihedral angles of 60 and 180° between the CH_2 protons and the Karplus correlation is therefore far closer to the observed coupling constants. The proton NMR spectrum for monoaldehyde **23** in $CDCl_3$ shows intermediary vicinal coupling constants for the $CHCH_2$ unit (J=5.3 and 8.0 Hz), indicating that conformation B is somewhat favored in this case as well. In all of these spectra, the geminal coupling for the 6-CH_2 is ca. 11 Hz. However, all three dipyrroles are drawn into a conformation of type A by strong hydrogen bonding interactions. These hydrogen bonding interactions are also evident from the downfield shifts for the two NH resonances in DMSO-d_6, showing values of 10.88 and 11.35 ppm for **20a**, 11.03 and 11.58 ppm for **23**, and 11.21 and 11.65 ppm for **22**. The increased deshielding observed for the dialdehyde is due to the increased electron-withdrawing characteristics of the formyl moieties compared to the ester units. Hence, the NMR data provides important insights into the factors that influence the favored conformations of dipyrrolic intermediates. As the dibenzyl ester **20a** appears to favor a different conformation to dialdehyde **22**, placement of the formyl units may affect the efficacy

Table 1
Chemical shifts and coupling constants for the $CHCH_2$ system in dipyrroles **20a**, **22**, and **23** in $CDCl_3$ or DMSO-d_6. The triplets observed in some cases for the 7-CH_x are unresolved doublets of doublets and the reported *J* values fall between the coupling constants for H_a–H_x and H_b–H_x

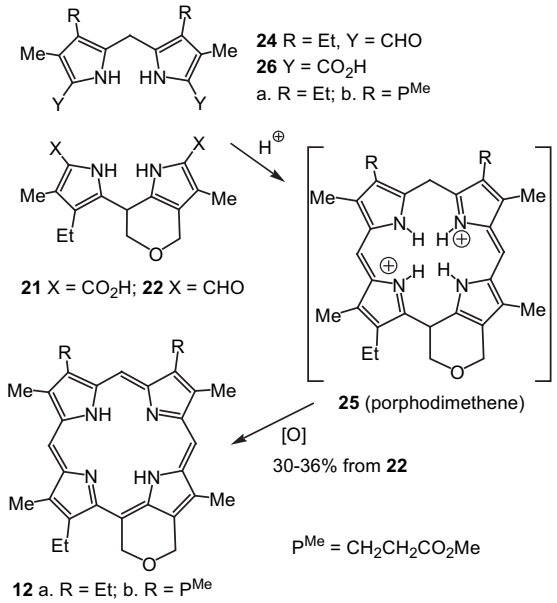
Dipyrrole (solvent)	6-CH_a (multiplicity, *J* Hz)	6-CH_b (multiplicity, *J* Hz)	7-CH (multiplicity, *J* Hz)
20a ($CDCl_3$)	3.78 (dd, 7.1, 11.0 Hz)	4.08 (dd, 5.0, 11.0 Hz)	4.21 (br t, 5.9 Hz)
20a (DMSO-d_6)	3.69 (dd, 6.3, 11.0 Hz)	3.92 (dd, 5.2, 11.0 Hz)	4.24 (t, 5.6 Hz)
22 ($CDCl_3$)	3.74 (dd, 9.5, 10.9 Hz)	4.14 (dd, 5.7, 10.9 Hz)	4.34 (dd, 5.7, 9.5 Hz)
22 (DMSO-d_6)	3.70 (dd, 6.8, 11.1 Hz)	3.96 (dd, 5.3, 11.1 Hz)	4.25 (t, 5.8 Hz)
23 ($CDCl_3$)	3.75 (dd, 8.0, 11.1 Hz)	4.09 (dd, 5.3, 11.1 Hz)	4.25 (dd, 5.5, 8.0 Hz)
23 (DMSO-d_6)	3.67 (dd, 7.5, 11.1 Hz)	3.93 (dd, 5.5, 11.1 Hz)	4.28 (br t, 6.5 Hz)

of macrocycle formation.[15–17] In earlier investigations, Gossauer demonstrated that a tripyrrane dialdehyde reacted with a dipyrrylmethane under acid catalyzed conditions to give pentaphyrin, but reaction of a dipyrrylmethane dialdehyde with a tripyrrane gave no pentapyrrolic product and only porphyrin by-products were noted.[24] No explanation was offered for this observation and in fact the result does not seem to be consistent with the



mechanism for the reaction. Initial condensation would be expected to give the same open-chain pentapyrrolic intermediate, so why should be the final outcome be different? Clearly, our results offer a possible answer if the conformations of the intermediates are altered when the formyl moieties are present on different reactants. Importantly, if the placement of formyl groups on a dipyrrolic fragment significantly alters the conformations, it may be possible to make use of this effect in directing macrocycle formation.

Initially, the synthesis of porphyrin **12a** was attempted using conventional MacDonald '2+2' condensation conditions[25] by reacting dipyrrole dicarboxylic acid **21** with dipyrrylmethane dialdehyde **24** in the presence of *p*-toluenesulfonic acid in methanol–dichloromethane (Scheme 6). The reaction generates the



Scheme 6.

tetrapyrrolic macrocycle as a porphodimethene **25**, but this undergoes slow air oxidation in the presence of excess zinc acetate. Although these conditions gave good yields for *meso*,β-propanoporphyrins **9**, very little of the porphyrin ether product **12a** was formed. Dropwise addition of the dipyrrolic reactants to a solution of *p*-toluenesulfonic acid in methanol–dichloromethane showed some improvement but the yield was only raised to 9%. Slow addition of the reactants to the acid catalyst allows the effective concentration of reactants to be minimized at any given time and this may facilitate cyclization reactions. However, this approach must be used with caution as acid catalyzed fragmentation–recombination processes may occur that can produce mixtures of porphyrin products.[26] The NMR data for the isolated product was consistent with a single isomer[27] and the slow addition method does not lead to undue difficulties in this case. However, the yields were still unacceptably low and further modifications were necessary. We speculated that the electron-withdrawing effect of the dihydropyran oxygen exerted a deleterious effect by deactivating the nearby pyrrolic unit towards electrophilic substitution. This factor had also lead to problems with the synthesis of dipyrroles **20** and the formylation of this system to give dialdehyde **22** also required the use of higher temperatures than were usually necessary. It is also possible that the conformation of the dipyrrolic intermediates was not conducive to macrocycle formation, but this factor is more difficult to address. If the electronic factor is primarily responsible for the low yields, better results would be expected using dialdehyde **22** and dipyrrylmethane **26a**. As dipyrrole **22** already has the required carbon–carbon bonds, it only remains for the more reactive dipyrrole **26a** to undergo electrophilic substitution to assemble the porphyrin macrocycle. Dipyrroles **22** and **26a** were condensed under the slow addition MacDonald '2+2' conditions and then air oxidized for 2 days in the presence of zinc acetate (Scheme 6). Following extraction, demetalation, chromatography and recrystallization from chloroform–methanol, the new porphyrin system was isolated in 36% yield. Dialdehyde **22** was also reacted with dipyrrylmethane **26b** under these conditions to give the related porphyrin diester **12b** in 30% yield. Although the successful synthetic route to porphyrins **12a** and **12b** is based on earlier work, various steps had to be considerably modified to overcome the deleterious effects due to the presence of an oxygen atom. Porphyrin synthesis is generally reliant on the electron-rich characteristics of the pyrrolic precursors, and electron-withdrawing groups can severely inhibit the necessary electrophilic substitution processes that lead to macrocycle formation. The observations and solutions to the issues that arose in the synthesis of dihydropyran-fused porphyrins have potential value in the synthesis of other porphyrins with electron-withdrawing groupings.

The UV–vis spectrum for porphyrin **12a** (Fig. 5) was very similar to the spectrum previously reported for **9** and gave a Soret band at 404 nm together with four Q bands in the visible region (phyllotype pattern[28]). Addition of TFA to solutions of **12a** gave the related dication **12a**H_2^{2+}, and this afforded a much stronger and sharper Soret absorption at 411 nm. The proton NMR spectrum of **12a** in $CDCl_3$ showed typical porphyrin-type aromatic characteristics[29] where the three external *meso*-protons gave rise to three 1H

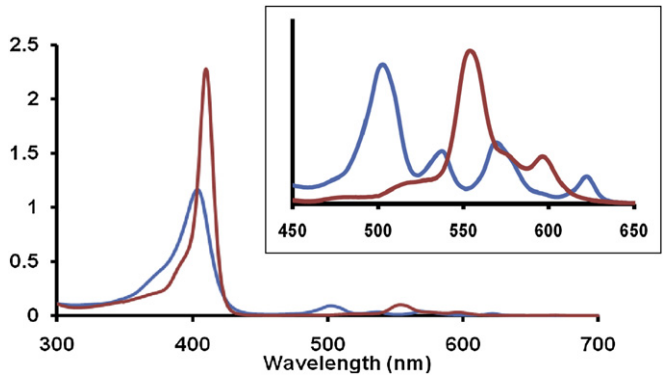


Figure 5. UV–vis spectra of porphyrin **12a** in 1% Et_3N–chloroform (free base; blue line) and 1% TFA–chloroform (dication **12a**H_2^{2+}; red line). The insert shows details of the Q band region.

singlets near 10 ppm, while the internal NHs gave two separate NH resonances at ca. 3.5 ppm. The appearance of two separate NH peaks indicates that a single tautomeric species is favored for **12a**, and that NH exchange is relatively slow. The resonances were somewhat concentration dependent and the *meso*-protons shifted upfield by approx. 0.1 ppm in more concentrated solutions. The exocyclic ring gave rise to two singlets at 5.87 and 6.86 ppm, which correspond to the pyrrole CH_2 and *meso*-CH_2 components, respectively. These large downfield shifts are consistent with the expected porphyrin diamagnetic ring current. The corresponding dication **12a**H_2^{2+} in TFA–$CDCl_3$ showed the *meso*-protons further downfield near 10.5 ppm, while up to four different NH resonances could be seen upfield between −2.5 and −3.7 ppm (Fig. 6). The singlets for the exocyclic ring were shifted slightly downfield by 0.1–0.2 ppm, and are now observed at 5.99 and 7.05 ppm. The resonances for the porphyrin methyls and the methylenes of the ethyl groups are also mostly shifted downfield, and taken together these data indicate that the dication has a slightly larger diatropic ring current than the free base porphyrin. Porphyrin **12b** gave

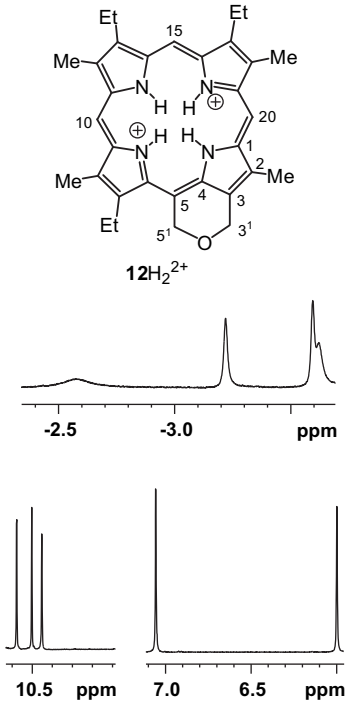


Figure 6. Partial 500 MHz proton NMR spectrum of porphyrin dication **12a**H_2^{2+} in TFA–$CDCl_3$ showing the downfield and upfield regions. The four internal NH protons give rise to four separate upfield resonances between −2.5 and −3.7 ppm.

similar UV and proton NMR data. Porphyrins **12a** and **12b** were also characterized by carbon-13 NMR spectroscopy, mass spectrometry, and combustion analysis.

3. Conclusions

Knorr-type reactions of tetrahydropyran-4-one with oximes derived from esters of acetoacetic acid in the presence of zinc dust and sodium propionate in propionic acid at 150–155 °C gave good yields of pyrroles with fused dihydropyran rings. These fused ring pyrroles exhibit unusual ^5J homonuclear coupling in their proton NMR spectra that are analogous to homoallylic coupling in olefinic systems. The dihydropyanopyrroles reacted with *N*-chlorosuccinimide in CCl_4 to give unstable 7-chloro-derivatives and these further condensed with an α-unsubstituted pyrrole under acid catalyzed conditions to give dipyrroles incorporating the dihydropyran unit. Cleavage of the protective ester groups gave a dicarboxylic acid, and subsequent treatment with TFA and trimethyl orthoformate afforded the related dialdehyde. The proton NMR spectra for the dihydropyran-linked dipyrroles demonstrated that significant conformational changes occur due to solvent interactions (DMSO vs $CHCl_3$) and the introduction of electron-withdrawing formyl moieties. The dihydropyran-linked dipyrrole dialdehyde was condensed with dipyrrylmethanes in the presence of *p*-toluenesulfonic acid, and following air oxidation in the presence of zinc acetate, the corresponding porphyrin ethers could be isolated in 30–36% yield. The formation of this unique porphyrin system suggests that related crown ether structures might also be obtained by using a similar synthetic strategy. This could potentially be achieved by using acyclic ketones with suitably placed methoxy groups as the precursors to pyrrolic intermediates. Alternatively, previously reported crown ether/cyclic ketone hydrids[30] could be used to directly synthesize pyrroles with fused crown ether units.

4. Experimental

4.1. General

Benzyl acetoacetate, *tert*-butyl acetoacetate, ethyl acetoacetate, tetrahydro-4*H*-pyan-4-one, 4-chromanone, *N*-chlorosuccinimide, *p*-toluenesulfonic acid, and 10% palladium/charcoal were purchased from Aldrich or Acros, and were used without further purification. Chromatography was performed using grade three neutral alumina or 70–230 mesh silica gel. Melting points were determined in open capillary tubes using a Mel-Temp apparatus and are uncorrected. UV–vis absorption spectra were run on a Varian Cary Spectrophotometer. Proton and carbon-13 NMR data were obtained on a Varian Gemini 400 MHz FT NMR spectrometer or a 500 MHz Bruker NMR Avance III spectrometer. Mass spectral determinations were conducted at the Mass Spectral Laboratory, School of Chemical Sciences, University of Illinois at Urbana-Champaign, and elemental analyses were obtained from the School of Chemical Sciences Microanalysis Laboratory at the University of Illinois.

4.2. Synthetic procedures

*4.2.1. Benzyl 3-methyldihydropyrano[4,3-b]pyrrole-2-carboxylate (**15b**).* Tetrahydro-4*H*-pyran-4-one (1.00 g, 10 mmol) and sodium propionate (13.4 g, 0.14 mol) were allowed to dissolve in propionic acid (224 mL) while heating to 150 °C. A solution of benzyl ester oxime **14b**[14b] (2.43 g, 11 mmol) in propionic acid (45 mL) was then added dropwise while simultaneously adding zinc dust (4.0 g, 61 mmol) in small portions, keeping the reaction mixture at a temperature between 150–155 °C. Once the addition was

completed, the resulting mixture was allowed to stir for 1 h while gradually cooling to 140 °C. The resulting orange mixture was cooled to 70 °C, then poured into ice-water (600 mL) and allowed to stand overnight. The precipitate was suction filtered and recrystallized from ethanol to give the dihydropyranopyrrole (797 mg, 2.94 mmol) as a tan powder, mp 123–125 °C. The aqueous filtrate was extracted with dichloromethane, washed with water and 10% aqueous sodium bicarbonate, and dried over sodium sulfate. The residue was combined with the filtrate from the recrystallization and purified by flash chromatography on silica, eluting with a 50:50 mixture of dichloromethane and chloroform. The product containing fractions were identified by TLC, combined, and rotary evaporated. The resulting solid was crystallized from ethanol to give the product (545 mg, 2.01 mmol, combined yield 50%) as pale yellow crystals, mp 124.5–125.5 °C; IR (Nujol): ν 3304 (NH str.), 1672 cm^{-1} (C=O str.); ^1H NMR (500 MHz, $CDCl_3$): δ 2.22 (3H, s), 2.67 (2H, t, J=5.6 Hz), 3.92 (2H, t, J=5.6 Hz), 4.60 (2H, br t, J=1.1 Hz), 5.31 (2H, s), 7.30–7.43 (5H, m), 8.87 (1H, br s); ^{13}C NMR ($CDCl_3$): δ 10.6, 23.9, 64.3, 64.6, 65.8, 117.7, 118.2, 124.0, 128.2, 128.3, 128.7, 129.1, 136.7, 161.7. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.31; N, 5.16. Found: C, 70.66; H, 6.35; N, 5.23.

*4.2.2. Ethyl 3-methyldihydropyrano[4,3-b]pyrrole-2-carboxylate (**15a**).* Tetrahydro-4*H*-pyran-4-one (2.50 g, 25 mmol) and sodium propionate (33.6 g, 0.35 mol) were allowed to dissolve in propionic acid (112 mL) upon heating to 150 °C. A solution of ethyl ester oxime **14a**[14b] (4.35 g, 27 mmol) in propionic acid (112 mL) was then added dropwise to the solution while small portions of zinc dust (10 g, 0.15 mol) were added simultaneously, maintaining the reaction mixture at a temperature between 150 °C and 155 °C. Once the addition was completed, the mixture was stirred for 1 h while allowing it to gradually cool to 110 °C. The resulting orange mixture was cooled to 70 °C, then poured into a 2 L beaker of ice-water (1.8 L) and allowed to stand overnight. The aqueous solution was saturated with sodium chloride and filtered. The resulting solid was chromatographed on flash silica, eluting with a 50:50 mixture of dichloromethane and chloroform. The product containing fractions were identified by TLC, combined, and evaporated under reduced pressure. Recrystallization from ethanol gave dihydropyranopyrrole **15a** (1.77 g, 8.47 mmol, 34%) as an off white solid, mp 145–146 °C; IR (Nujol): ν 3306, 3263 (NH str.), 1654 cm^{-1} (C=O str.); ^1H NMR (500 MHz, $CDCl_3$): δ 1.35 (3H, t, J=7.1 Hz), 2.20 (3H, s), 2.70 (2H, tt, J=1.2, 5.5 Hz), 3.93 (2H, t, J=5.5 Hz), 4.30 (2H, q, J=7.1 Hz), 4.60 (2H, t, J=1.2 Hz), 8.60 (1H, br s); ^1H NMR (500 MHz, DMSO-d_6): δ 1.25 (3H, t, J=7.1 Hz), 2.09 (3H, s), 2.56 (2H, br t, J=5.6 Hz), 3.77 (2H, t, J=5.6 Hz), 4.18 (2H, q, J=7.1 Hz), 4.46 (2H, br t, J=1.2 Hz), 11.18 (1H, br s); ^{13}C NMR ($CDCl_3$): δ 10.5, 14.7, 23.9, 60.0, 64.3, 64.6, 118.05, 118.06, 123.4, 128.8, 162.2. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.22; N, 6.69. Found: C, 62.96; H, 7.28; N, 6.67.

*4.2.3. tert-Butyl 3-methyldihydropyrano[4,3-b]pyrrole-2-carboxylate (**15c**).* Tetrahydro-4*H*-pyran-4-one (1.00 g, 10 mmol) and sodium propionate (13.4 g, 0.14 mol) were allowed to dissolve in propionic acid (112 mL) while heating to 150 °C. A solution of *tert*-butyl ester oxime **14c**[14b] (2.06 g, 11 mmol) in propionic acid (45 mL) was added dropwise while zinc dust (4.0 g, 61 mmol) was added simultaneously in small portions, and the reaction mixture was maintained at a temperature between 150–155 °C. Once the addition was complete, the mixture was allowed to stir for 10 min while maintaining the temperature between 150–155 °C. The resulting orange mixture was cooled to 70 °C, then poured into 600 mL of ice-water and allowed to stand overnight. The aqueous solution was extracted with dichloromethane (×3), and the combined organic solutions were washed with water and saturated aqueous sodium bicarbonate solution, and then dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica, eluting with a 50:50 dichloromethane–chloroform. The product containing fractions were identified by TLC, combined, and evaporated. The resulting solid was further recrystallized from ethanol to give the *tert*-butyl ester (471 mg, 1.99 mmol, 20%) as pale yellow crystals, mp 185–186 °C; IR (Nujol): ν 3308 (NH str.), 1663 cm^{-1} (C=O str.); ^1H NMR (500 MHz, $CDCl_3$): δ 1.56 (9H, s), 2.17 (3H, s), 2.69 (2H, t, J=5.6 Hz), 3.92 (2H, t, J=5.6 Hz), 4.60 (2H, t, J=1.1 Hz), 8.71 (1H, br s); ^{13}C NMR ($CDCl_3$): δ 10.6, 24.0, 28.7, 64.4, 64.7, 80.6, 117.9, 119.3, 122.5, 128.1, 161.8. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.55; H, 8.21; N, 5.97.

*4.2.4. Ethyl 3-methylchromano[4,3-b]pyrrole-2-carboxylate (**17**).* A mixture of 4-chromanone (1.85 g, 12.5 mmol) and sodium propionate (16.8 g, 0.175 mmol) in propionic acid (56 mL) was prepared and heated while stirring to 150 °C. A solution of ethyl ester oxime **14a**[14b] (2.17 g, 13.6 mmol) in propionic acid (56 mL) was then added dropwise while zinc dust (5.0 g, 76 mmol) was simultaneously added in small portions, maintaining the reaction mixture at a temperature between 150 °C and 155 °C. Once the addition was completed, the resulting mixture was allowed to stir for 10 min while maintaining the temperature between 150 °C and 155 °C. The resulting mixture was further cooled to 70 °C, then poured into a beaker of ice-water and allowed to stand overnight for full precipitation. The mixture was filtered, and the solid was recrystallized from 100% ethanol to give the chromanopyrrole (160 mg, 0.623 mmol) as an off-white solid, mp 184–185 °C. The aqueous solution was also extracted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The extract was then combined with the filtrate from the recrystallization and chromatographed on flash silica, eluting with dichloromethane. The product containing fractions were evaporated under reduced pressure and the residue recrystallized from ethanol to gave the tricyclic pyrrole (15 mg, 0.058 mmol) (overall yield 5.5%) as a white solid, mp 184–185 °C; IR (Nujol): ν 3287 (NH str.), 1660 cm^{-1} (C=O str.); ^1H NMR (500 MHz, $CDCl_3$): δ 1.40 (3H, t, J=7.1 Hz), 2.27 (3H, s), 4.38 (2H, q, J=7.1 Hz), 5.26 (2H, s), 6.91–6.95 (2H, m), 7.13 (1H, td, J=1.5, 7.7 Hz), 7.36 (1H, d, J=7.7 Hz), 9.40 (1H, br s); ^{13}C NMR ($CDCl_3$): δ 10.7, 14.8, 60.5, 65.0, 116.1, 117.1, 117.3, 120.6, 120.7, 121.6, 123.7, 127.2, 129.1, 153.9, 162.2. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.88; H, 5.86; N, 5.52.

*4.2.5. Benzyl 7(5-benzyloxycarbonyl-3-ethyl-4-methyl-2-pyrrolyl)-3-methyldihydropyrano[4,3-b]pyrrole-2-carboxylate (**20a**).* Benzyl ester **15b** (200 mg, 0.738 mmol) was dissolved in carbon tetrachloride (20 mL), *N*-chlorosuccinimide (100 mg, 0.749 mmol) was added, and the mixture was stirred under a 250 W lamp for 2.5 h. The resulting solution was diluted with dichloromethane, washed with water, and 5% aqueous sodium bicarbonate, and the organic layer dried over sodium sulfate and rotary evaporated to give the crude chlorinated derivative **18b** as an orange oil. The crude oil was dissolved in acetic acid (7 mL) along with α-free pyrrole **19**[31,32] (162 mg, 0.667 mmol) and allowed to stir for 2 h in the presence of *p*-toluenesulfonic acid monohydrate (19 mg, 0.10 mmol). The solution was diluted with dichloromethane, washed with water and 5% aqueous sodium bicarbonate, and dried over sodium sulfate. The organic solvent was then removed under reduced pressure and the residue chromatographed on a silica column, eluting with chloroform. The product fractions were identified by TLC, combined, and rotary evaporated. Further purification by recrystallization from ethanol gave the title dipyrrole (185 mg, 0.36 mmol, 54%) as a white powder, mp 189–190 °C; IR (Nujol): ν 3293, 3227 (NH str.), 1672, 1655 cm^{-1} (C=O str.); ^1H NMR (500 MHz, $CDCl_3$): δ 1.10 (3H, t, J=7.5 Hz), 2.21 (3H, s), 2.27 (3H, s), 2.42–2.51 (2H, m), 3.78 (1H, dd, J=7.1, 11.0 Hz), 4.08 (1H, dd, J=5.0,

11.0 Hz), 4.21 (1H, br t, J=5.9 Hz), 4.66–4.75 (2H, AB quartet, J=13.5 Hz), 5.12–5.19 (2H, m), 5.26 (1H, s), 5.28 (1H, s), 7.28–7.39 (10H, m), 9.26 (1H, br s), 9.35 (1H, br s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.77 (3H, t, J=7.3 Hz), 1.86–1.95 (1H, m), 2.07–2.16 (1H, m), 2.15 (3H, s), 2.16 (3H, s), 3.69 (1H, dd, J=6.3, 11.0 Hz), 3.92 (1H, dd, J=5.2, 11.0 Hz), 4.23 (1H, t, J=5.6 Hz), 4.53–4.61 (2H, AB quartet, J=13.8 Hz), 5.21–5.28 (4H, m), 7.27–7.42 (10H, m), 10.88 (1H, s), 11.35 (1H, s); ^{13}C NMR ($CDCl_3$): δ 10.96, 10.99, 16.8, 17.6, 33.2, 64.8, 65.9, 66.0, 70.4, 118.4, 118.56, 118.65, 123.0, 125.3, 126.4, 128.0, 128.18, 128.23, 128.71, 128.73, 130.5, 130.8, 136.3, 136.4, 162.1, 162.2. HRMS (EI), m/z calcd for $C_{31}H_{32}N_2O_5$: 512.2311. Found: 512.2314. Anal. Calcd for $C_{31}H_{32}N_2O_5\cdot$½H_2O: C, 71.38; H, 6.37; N, 5.37. Found: C, 71.35; H, 6.33; N, 5.32.

*4.2.6. 7(5-Carboxy-3-ethyl-4-methyl-2-pyrrolyl)-3-methyldihydropyrano[4,3-b]pyrrole-2-carboxylic acid (**21**).* Dibenzyl ester **20a** (500 mg, 0.977 mmol), reagent grade acetone (150 mL), methanol (20 mL), and triethylamine (20 drops) were added to a hydrogenation vessel. Palladium of 10% on activated charcoal (200 mg) was added to the vessel under nitrogen, and the mixture was allowed to shake under a hydrogen atmosphere (40 psi) overnight. The palladium catalyst was then removed by suction filtration and the solution was rotary evaporated. The resulting oil was dissolved in 5% aqueous ammonia and then enough water was added to the solution to give a total volume of 40 mL. This aqueous solution was then cooled to <5 °C in a salt–ice bath and neutralized to litmus with glacial acetic acid while maintaining the temperature <5 °C. The resulting cloudy solution was allowed to stand at below 5 °C to allow full precipitation, then suction filtered, washed repeatedly with water, and vacuum dried to give the dicarboxylic acid (323 mg, 0.973 mmol, 99%) as a pale purple solid, mp 162 °C, dec; ^{1}H NMR (DMSO-d_6): δ 0.82 (3H, t, J=7.4 Hz), 1.93–2.02 (1H, m), 2.10–2.22 (1H, m), 2.14 (3H, s), 2.15 (3H, s), 3.70 (1H, dd, J=6.0, 11.0 Hz), 3.88 (1H, dd, J=5.0, 11.0 Hz), 4.15 (1H, br t, J=5.4 Hz), 4.52–4.61 (2H, AB quartet, J=13.3 Hz), 10.43 (1H, br s), 11.08 (1H, br s), 11.91 (2H, br s); ^{13}C NMR (DMSO-d_6): δ 10.3, 10.5, 15.6, 16.7, 32.9, 63.8, 69.9, 117.44, 117.49, 118.3, 121.4, 123.3, 125.5, 129.5, 131.9, 162.6, 162.7. Anal. Calcd for $C_{17}H_{20}N_2O_5\cdot$¼H_2O: C, 60.61; H, 6.13; N, 8.32. Found: C, 60.70; H, 6.14; N, 8.18.

*4.2.7. 7(3-Ethyl-5-formyl-4-methyl-2-pyrrolyl)-3-methyldihydropyrano[4,3-b]pyrrole-2-carbaldehyde (**22**).* Dibenzyl ester **20a** (250 mg, 0.488 mmol) was hydrogenated under the foregoing conditions, the catalyst was suction filtered and the solvent evaporated on a rotary evaporator. The residue was dried overnight under vacuum and gave the dicarboxylic acid **21** (165 mg) as an off-white solid in quantitative yield. This was dissolved in TFA (3 mL) and stirred at room temperature for 2 min. Trimethyl orthoformate (0.60 mL, 5.5 mmol) was added dropwise while maintaining the temperature at 25 °C (±2 °C), and then allowed to stir for an additional 10 min on a preheated water bath at 40 °C. The solution was then poured into ice-water (80 mL), and neutralized with aqueous ammonia. The resulting mixture was extracted with dichloromethane, dried over sodium sulfate, and evaporated under reduced pressure. The dark residue was purified by column chromatography on silica, eluting with 20–30% ethyl acetate in toluene. The product fractions were combined, and the solvent was evaporated under reduced pressure to give the dialdehyde as a brown solid (117.8 mg, 0.393 mmol, 80%). Recrystallization from ethyl acetate–hexanes gave dipyrrole dialdehyde (89.3 mg, 0.298 mmol, 61%) as an off-white solid, mp 177 °C, dec; IR (Nujol): ν 3215 (NH str.), 1634 cm^{-1} (C=O str.); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (3H, t, J=7.6 Hz), 2.24 (3H, s), 2.29 (3H, s), 2.47 (2H, q, J=7.6 Hz), 3.74 (1H, dd, J=9.5, 10.9 Hz), 4.14 (1H, dd, J=5.7, 10.9 Hz), 4.34 (1H, dd, J=5.7, 9.5 Hz), 4.65–4.75 (2H, AB quartet, J=13.5 Hz), 9.09 (1H, s), 9.11 (1H, s), 10.46 (1H, br s), 10.89 (1H, br s); ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.86 (3H, t, J=7.4 Hz), 2.02–2.12 (1H, m), 2.14–2.28 (1H, m), 2.200 (3H, s), 2.203 (3H, s), 3.31 (3H, s), 3.70 (1H, dd, J=6.8, 11.1 Hz), 3.96 (1H, dd, J=5.3, 11.1 Hz), 4.25 (1H, t, J=5.8 Hz), 4.61 (2H, s), 9.50 (1H, s), 9.52 (1H, s), 11.21 (1H, s), 11.62 (1H, s); ^{13}C NMR ($CDCl_3$): δ 9.0, 9.1, 15.7, 17.1, 33.4, 64.3, 69.3, 119.9, 126.9, 127.2, 129.2, 129.3, 131.0, 135.5, 135.7, 176.0, 176.3. HRMS (EI), m/z calcd for $C_{17}H_{20}N_2O_3$: 300.1474. Found: 300.1470. Anal. Calcd for $C_{17}H_{20}N_2O_3\cdot$¼H_2O: C, 66.98; H, 6.78; N, 9.19. Found: C, 66.92; H, 6.66; N, 9.08.

*4.2.8. 7(5-Benzyloxycarbonyl-3-ethyl-4-methyl-2-pyrrolyl)-3-methyldihydropyrano[4,3-b]pyrrole-2-carbaldehyde (**23**).* *tert*-Butyl ester **15b** (200 mg, 0.844 mmol) was dissolved in carbon tetrachloride (16 mL) along with *N*-chlorosuccinimide (113 mg, 0.844 mmol), and stirred under a 250 W lamp for 200 min. The solution was diluted with dichloromethane, washed with water and 5% aqueous sodium bicarbonate, dried over sodium sulfate, and rotary evaporated to give the crude chlorinated derivative **18c** as a red-orange oil. The oil was dissolved in acetic acid (7 mL) along with α-free pyrrole **19**[31,32] (161 mg, 0.66 mmol) and allowed to stir for 2 h in the presence of *p*-toluenesulfonic acid (11 mg, 0.06 mmol). The resulting solution was diluted with dichloromethane, washed with water and 5% aqueous sodium bicarbonate, and dried over sodium sulfate. The organic solvent was then evaporated under reduced pressure and the residue was chromatographed on a silica column, eluting with a 50:50 mixture of dichloromethane and chloroform. The product fractions were rotary evaporated to give crude dipyrrole **20b** (316 mg, 0.66 mmol) as a dark red oil that was used without further purification. The oil was dissolved in trifluoroacetic acid (5 mL) and stirred for 1 h at room temperature. Trimethyl orthoformate (1.0 mL, 9.1 mmol) was added dropwise to the solution while maintaining the temperature below 30 °C and allowed to stir at room temperature for 1 h. The solution was poured into a beaker of ice-water (40 mL) and concentrated aqueous ammonia (5 mL) was added. The mixture was suction filtered to give a solid that was purified by silica column chromatography, eluting with 10% ethyl acetate–toluene. The product fractions were combined, and the solvent was evaporated under reduced pressure to give an oil. Crystallization from ethyl acetate–hexanes gave the aldehyde (46 mg, 0.113 mmol, 17%) as a tan solid, mp 90 °C, dec; IR (Nujol): ν 3237 (NH str.), 1668, 1627 cm^{-1} (C=O str.); ^{1}H NMR ($CDCl_3$): δ 1.12 (3H, t, J=7.6 Hz), 2.22 (3H, s), 2.28 (3H, s), 2.47 (2H, q, J=7.6 Hz), 3.75 (1H, dd, J=8.0, 11.1 Hz), 4.09 (1H, dd, J=5.3, 11.1 Hz), 4.25 (1H, dd, J=5.5, 8.0 Hz), 4.70 (2H, s), 5.12 (1H, d, J=12.6 Hz), 5.26 (1H, d, J=12.6 Hz), 7.29–7.38 (5H, m), 9.27 (1H, s), 9.45 (1H, br s), 9.91 (1H, s); ^{1}H NMR (DMSO-d_6): δ 0.78 (3H, t, J=7.5 Hz), 1.92–2.00 (1H, m), 2.10–2.17 (1H, m), 2.16 (3H, s), 2.19 (3H, s), 3.67 (1H, dd, J=7.5, 11.1 Hz), 3.93 (1H, dd, J=5.5, 11.1 Hz), 4.28 (1H, br t, J=6.5 Hz), 4.56–4.63 (2H, AB quartet, J=13.8 Hz), 5.22–5.28 (2H, AB quartet, J=12.8 Hz), 7.30–7.42 (5H, m), 9.50 (1H, s), 11.03 (1H, br s), 11.58 (1H, s); ^{13}C NMR ($CDCl_3$): δ 9.1, 11.0, 16.4, 17.5, 33.3, 64.4, 66.0, 69.9, 118.5, 119.4, 125.9, 126.1, 127.5, 127.9, 128.2, 128.7, 129.2, 130.4, 135.6, 136.3, 162.3, 176.3. HRMS (EI), m/z calcd for $C_{24}H_{26}N_2O_4$: 406.1893. Found: 406.1891.

*4.2.9. 7,13,17-Triethyl-2,8,12,18-tetramethyl-3,5-(2-oxapropano)porphyrin (**12a**).* A solution of *p*-toluenesulfonic acid monohydrate (80 mg, 0.42 mmol) in dichloromethane (30 mL) and methanol (6 mL) was prepared in a 250 mL round bottom flask that was wrapped in foil. Dipyrrole dialdehyde **22** (39.1 mg, 0.13 mmol) and dipyrrole dicarboxylic acid **26a**[33] (43.6 mg, 0.137 mmol) were dissolved in dichloromethane (24 mL) and methanol (1.5 mL), and this solution was added slowly dropwise to the reaction flask over 1 h. The solution was allowed to stir overnight in the dark, then a saturated solution of zinc acetate in methanol (2 mL) was added, and the reaction was allowed to stir for a further 2 days open to the air for oxidation. The resulting solution was washed with water and

carefully back extracted with chloroform. The organic solvent was then evaporated, and the residue was dissolved in trifluoroacetic acid (5 mL), diluted with chloroform, and washed with water and 5% aqueous sodium bicarbonate. The solvent was removed via rotary evaporation and the residue was chromatographed on grade 3 neutral alumina, eluting with dichloromethane. The product fractions were combined and rotary evaporated, and subsequent recrystallization from chloroform and methanol gave the porphyrin six-membered cyclic ether (23.2 mg, 0.047 mmol, 36%) as a dark purple powder, mp 250 °C, dec; UV–vis (1% Et_3N–$CHCl_3$): λ_{max} ($\log_{10}\epsilon$) 404 (5.23), 502 (4.14), 537 (3.71), 569 (3.78), 622 nm (3.45); UV–vis (1% TFA–$CHCl_3$): λ_{max} ($\log_{10}\epsilon$) 411 (5.53), 554 (4.18), 597 nm (3.67); ^{1}H NMR (500 MHz, $CDCl_3$): δ −3.60 (1H, br s), -3.46 (1H, br s), 1.77 (3H, t, J=7.7 Hz), 1.86 (3H, t, J=7.7 Hz), 1.88 (3H, t, J=7.7 Hz), 3.48 (3H, s), 3.56 (3H, s), 3.60 (3H, s), 3.64 (3H, s), 3.90 (2H, q, J=7.7 Hz), 4.00 (2H, q, J=7.7 Hz), 4.11 (2H, q, J=7.7 Hz), 5.87 (2H, s), 6.86 (2H, s), 9.95 (1H, s), 9.98 (1H, s), 10.04 (1H, s); ^{1}H NMR (500 MHz, TFA–$CDCl_3$): δ −3.56 (1H, br s), −3.53 (1H, br s), −3.16 (1H, br s), −2.51 (1H, br s), 1.70 (3H, t, J=7.9 Hz), 1.75 (3H, t, J=7.9 Hz), 1.78 (3H, t, J=7.7 Hz), 3.55 (3H, s), 3.56 (3H, s), 3.62 (3H, s), 3.63 (3H, s), 3.91 (2H, q, J=7.7 Hz), 4.09 (2H, q, J=7.9 Hz), 4.11 (2H, q, J=7.9 Hz), 5.99 (2H, s), 7.05 (2H, s), 10.44 (1H, s), 10.49 (1H, s), 10.57 (1H, s); ^{13}C NMR ($CDCl_3$): δ 11.6, 11.77, 11.80, 11.9, 16.6, 17.7, 18.0, 19.9, 20.1, 22.2, 66.9, 69.1, 95.8, 96.8, 97.1, 112.7, 112.7, 132.5, 133.4, 135.5, 135.6, 138.1, 138.2, 140.1, 144.5; ^{13}C NMR (TFA–$CDCl_3$): δ 11.8, 11.9, 12.0, 15.9, 16.47, 16.52, 20.24, 20.29, 21.7, 65.1, 69.4, 97.3, 98.4, 99.9, 132.4, 135.9, 137.0, 138.0, 138.5, 138.8, 139.0, 141.0, 141.4, 141.7, 142.6, 142.9, 143.0, 143.1, 144.1, 145.0. HRMS (EI), m/z calcd for $C_{32}H_{36}N_4O$: 492.2889. Found: 492.2887. Anal. Calcd for $C_{32}H_{36}N_4O\cdot{}^1/_{20}CHCl_3$: C, 77.20; H, 7.29; N, 11.24. Found: C, 77.44; H, 7.46; N, 11.14.

*4.2.10. 7-Ethyl-13,17-di(2-methoxycarbonylethyl)-2,8,12,18-tetramethyl-3,5-(2-oxapropano) porphyrin (**12b**).* Dialdehyde **22** (39.1 mg, 0.13 mmol) and dipyrrole dicarboxylic acid **26b**[33] (60.0 mg, 0.14 mmol) were reacted under the foregoing conditions. Following purification of a grade 3 alumina column, eluting with dichloromethane, the product was recrystallized from chloroform–methanol to give the diester (23.8 mg, 0.039 mmol, 30%) as a purple solid, mp 258–259 °C; UV–vis (1% Et_3N–$CHCl_3$): λ_{max} ($\log_{10}\epsilon$) 405 (5.29), 503 (4.20), 537 (3.81), 570 (3.87), 623 nm (3.61); UV–vis (1% TFA–$CHCl_3$): λ_{max} ($\log_{10}\epsilon$) 412 (5.53), 555 (4.22), 597 nm (3.76); ^{1}H NMR (500 MHz, $CDCl_3$): δ −3.59 (1H, s), −3.44 (1H, s), 1.78 (3H, t, J=7.7 Hz), 3.24–3.32 (4H, m), 3.49 (3H, s), 3.58 (3H, s), 3.63 (3H, s), 3.66 (3H, s), 3.67 (3H, s), 3.69 (3H, s), 3.94 (2H, q, J=7.7 Hz), 4.33 (2H, t, J=7.9 Hz), 4.44 (2H, t, J=7.8 Hz), 5.90 (2H, s), 6.90 (2H, s), 9.96 (1H, s), 10.01 (1H, s), 10.06 (1H, s); ^{1}H NMR (500 MHz, TFA–$CDCl_3$): δ −3.42 (1H, s), −3.40 (1H, br s), −3.00 (1H, s), −2.41 (1H, br s), 1.77 (3H, t, J=7.7 Hz), 3.12 (2H, t, J=7.5 Hz), 3.18 (2H, t, J=7.5 Hz), 3.54 (3H, s), 3.56 (3H, s), 3.580 (3H, s), 3.581 (3H, s), 3.64 (3H, s), 3.65 (3H, s), 3.90 (2H, q, J=7.7 Hz), 4.41–4.47 (4H, m), 5.98 (2H, s), 7.04 (2H, s), 10.49 (1H, s), 10.57 (1H, s), 10.79 (1H, s); ^{13}C NMR (TFA–$CDCl_3$): δ 11.8, 12.0, 12.2, 15.9, 21.67, 21.74, 21.80, 35.57, 35.61, 52.5, 65.0, 67.5, 98.43, 98.47, 100.0, 115.7, 132.1, 136.0, 137.6, 138.4, 138.7, 139.1, 139.6, 139.8, 140.7, 141.1, 141.2, 141.4, 142.4, 142.7, 142.9, 143.0, 174.2. HRMS (EI), m/z calcd for $C_{36}H_{40}N_4O_5$: 608.2999. Found: 608.3013. Anal. Calcd for $C_{36}H_{40}N_4O_5$: C, 71.03; H, 6.62; N, 9.20. Found: C, 70.71; H, 6.91; N, 8.82.

Acknowledgements

This work was supported by the National Science Foundation under grant nos. CHE-0616555 and CHE-0911699, and the Petroleum Research Fund, administered by the American Chemical Society. B.E.S. also acknowledges support from Pfizer, Inc. Funding for a 500 MHz NMR spectrometer was provided by the National Science Foundation under grant no. CHE-0722385.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.069.

References and notes

1. Baker, E. W.; Palmer, S. E. In *The Porphyrins*; Dolphin, D., Ed.; Academic: New York, NY, 1978; Vol. 1, pp 486–552.
2. (a) Filby, R. H.; Van Berkel, G. J. In *Metal Complexes in Fossil Fuels. Geochemistry, Characterization, and Processing*; Filby, R. H., Branthaver, J. F., Eds.; American Chemical Society: Washington, DC, 1987; pp 2–37; (b) Callot, H. J. In *The Chlorophylls*; Scheer, H., Ed.; CRC: Boca Raton, 1991; pp 339–364; (c) Callot, H. J.; Ocampo, R. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic: San Diego, 2000; Vol. 1, pp 349–398; (d) Czernuszewicz, R. S. *J. Porphyrins Phthalocyanines* **2000**, *4*, 426.
3. (a) Chicarelli, M. I.; Kaur, S.; Maxwell, J. R. In *Metal Complexes in Fossil Fuels. Geochemistry, Characterization, and Processing*; Filby, R. H., Branthaver, J. F., Eds.; American Chemical Society: Washington, DC, 1987; pp 40–67; (b) Ocampo, R.; Callot, H. J.; Albrecht, P. In *Metal Complexes in Fossil Fuels. Geochemistry, Characterization, and Processing*; Filby, R. H., Branthaver, J. F., Eds.; American Chemical Society: Washington, DC, 1987; pp 68–73.
4. (a) Quirke, J. M. E.; Maxwell, J. R. *Tetrahedron* **1980**, *36*, 3453; (b) Fookes, C. J. R. *J. Chem. Soc., Chem. Commun.* **1985**, 706; (c) Chicarelli, M. I.; Wolff, G. A.; Maxwell, J. R. *J. Chem. Soc., Chem. Commun.* **1985**, 723; (d) Krane, J.; Skjetne, T.; Telnaes, N.; Bjoroy, M.; Schou, L.; Solli, H. *Tetrahedron* **1983**, *39*, 4109; (e) Bonnett, R.; Burke, P. J. *Geochim. Cosmochim. Acta* **1985**, *49*, 1487; (f) Boreham, C. J.; Fookes, C. J. R.; Popp, B. N.; Hayes, J. M. *Geochim. Cosmochim. Acta* **1989**, *53*, 2451; (g) Huseby, B.; Barth, T.; Ocampo, R. *Org. Geochem.* **1996**, *25*, 273.
5. (a) Freeman, D. H.; Saint Martin, D. C.; Boreham, C. J. *Energy Fuels* **1993**, *7*, 194; (b) Laycock, J. D.; Yost, R. A.; Wang, L.; Quirke, J. M. E. *Energy Fuels* **1995**, *9*, 1079.
6. Cantú, R.; Stencel, J. R.; Czernuszewicz, R. S.; Jaffé, P. R.; Lash, T. D. *Environ. Sci. Technol.* **2000**, *34*, 192.
7. Czernuszewicz, R. S.; Maes, E. M.; Rankin, J. G. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic: San Diego, 2000; Vol. 7, pp 293–337.
8. (a) Rankin, J. G.; Czernuszewicz, R. S.; Lash, T. D. *Org. Geochem.* **1995**, *23*, 419; (b) Rankin, J. G.; Czernuszewicz, R. S.; Lash, T. D. *Inorg. Chem.* **1995**, *34*, 3025; (c) Czernuszewicz, R. S.; Rankin, J. G.; Lash, T. D. *Inorg. Chem.* **1996**, *35*, 199; (d) Rankin, J. G.; Cantú, R.; Czernuszewicz, R. S.; Lash, T. D. *Org. Geochem.* **1999**, *30*, 201; (e) Boggess, J. M.; Czernuszewicz, R. S.; Lash, T. D. *Org. Geochem.* **2002**, *33*, 1111; (f) Czader, A.; Czernuszewicz, R. S. *Org. Geochem.* **2007**, *38*, 250.
9. Flaugh, M. E.; Rapoport, H. *J. Am. Chem. Soc.* **1968**, *90*, 6877.
10. (a) Chaudry, I. A.; Clezy, P. S.; Mirza, A. H. *Aust. J. Chem.* **1980**, *33*, 1095; (b) Smith, K. M.; Langry, K. C.; Minnetian, O. M. *J. Org. Chem.* **1984**, *49*, 4602; (c) Bauder, C.; Ocampo, R.; Callot, H. J. *Tetrahedron* **1992**, *48*, 5135.
11. (a) Clezy, P. S.; Fookes, C. J. R.; Prashar, J. K.; Salek, A. *Aust. J. Chem.* **1992**, *45*, 703; (b) Bong, I. C. C.; Clezy, P. S.; Fookes, C. J. R.; Prashar, J. K.; Salek, A. *Aust. J. Chem.* **1993**, *46*, 1193; (c) Clezy, P. S.; Leung, C. W. F. *Aust. J. Chem.* **1993**, *46*, 1705; (d) Atkinson, E. J.; Clezy, P. S.; Leung, C. W. F.; Ramadan, S.; Salek, A.; Zhuo, M. *Aust. J. Chem.* **1995**, *48*, 1873; (e) Clezy, P. S.; Salek, A. *Aust. J. Chem.* **1996**, *49*, 265.
12. (a) Baker, E. W.; Corwin, A. H.; Klesper, E.; Wei, P. E. *J. Org. Chem.* **1968**, *33*, 3144; (b) Verne-Mismer, J.; Ocampo, R.; Callot, H. J.; Albrecht, P. *Tetrahedron Lett.* **1986**, *27*, 5257; (c) Smith, N. W.; Smith, K. M. *Energy Fuels* **1990**, *4*, 675.
13. (a) Lash, T. D. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI: Greenwich, Connecticut, 1995; Vol. 1, pp 19–51; (b) Lash, T. D. *Org. Geochem.* **1989**, *14*, 213; (c) Lash, T. D.; Balasubramaniam, R. P.; Catarello, J. J.; Johnson, M. C.; May, D. A., Jr.; Bladel, K. A.; Feeley, J. M.; Hoehner, M. C.; Marron, T. G.; Nguyen, T. H.; Perun, T. J., Jr.; Quizon, D. M.; Shiner, C. M.; Watson, A. *Energy Fuels* **1990**, *4*, 668.
14. (a) Lash, T. D.; Catarello, J. J. *Tetrahedron* **1993**, *49*, 4159; (b) Quizon-Colquitt, D. M.; Lash, T. D. *J. Heterocycl. Chem.* **1993**, *30*, 477; (c) Li, W.; Lash, T. D. *Tetrahedron Lett.* **1998**, *39*, 8571; (d) Lash, T. D.; Quizon-Colquitt, D. M.; Shiner, C. M.; Nguyen, T. H.; Hu, Z. *Energy Fuels* **1993**, *4*, 668; (e) Zhang, B.; Lash, T. D. *Tetrahedron Lett.* **2003**, *44*, 7253; (f) Lash, T. D.; Li, W.; Quizon-Colquitt, D. M. *Tetrahedron* **2007**, *63*, 12324.
15. (a) Lash, T. D.; Bladel, K. A.; Johnson, M. C. *Tetrahedron Lett.* **1987**, *28*, 1135; (b) Lash, T. D.; Bladel, K. A.; Shiner, C. M.; Zajeski, D. L.; Balasubramaniam, R. P. *J. Org. Chem.* **1992**, *57*, 4809; (c) Lash, T. D.; Balasubramaniam, R. P. *Tetrahedron Lett.* **1990**, *31*, 7545; (d) Shiner, C. M.; Lash, T. D. *Tetrahedron* **2005**, *61*, 11628.
16. (a) Lash, T. D. *Tetrahedron Lett.* **1988**, *29*, 6877; (b) Lash, T. D. *Tetrahedron* **1998**, *54*, 359.
17. (a) Lash, T. D.; Johnson, M. C. *Tetrahedron Lett.* **1989**, *30*, 5697; (b) Lash, T. D.; Perun, T. J., Jr. *Tetrahedron Lett.* **1987**, *28*, 6265; (c) Lash, T. D.; Nguyen, T. H.; Hu, Z. *Synlett* **1994**, 905; (d) Hu, Z.; Lash, T. D. *Synlett* **1994**, 909; (e) Bastian, J. A.; Lash, T. D. *Tetrahedron* **1998**, *54*, 6299; (f) Chen, S.; Lash, T. D. *J. Heterocycl. Chem.* **1997**, *34*, 273; (g) Lash, T. D.; Chen, S. *Tetrahedron* **2005**, *61*, 11577; (h) Lash, T. D.; Marron, T. G.; Bastian, J. A. *Tetrahedron* **2007**, *63*, 12343.
18. Gribble, G. W. Knorr and Paal–Knorr pyrrole syntheses. In *Name Reactions in Heterocyclic Chemistry*; Li, J. J., Ed.; Wiley: Hoboken, NJ, 2005; pp 79–88.

19. Thanaval, V.; Krishnan, V. *J. Am. Chem. Soc.* **1982**, *104*, 3643.
20. For examples of porphyrins with appended crown ether units, see: (a) Gunter, M. J.; Johnston, M. R.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1009; (b) Gunter, M. J.; Johnston, M. R. *Tetrahedron Lett.* **1992**, *33*, 1771; (c) Kubo, Y.; Murai, Y.; Yamanaka, J.-i.; Tokita, S.; Ishimaru, Y. *Tetrahedron Lett.* **1999**, *40*, 6019; (d) Jahan, M.; Safaria, N.; Khosravia, H.; Moghimi, A.; Notash, B. *Polyhedron* **2005**, *24*, 1682; (e) Liu, Y.-C.; Kuo, M.-C.; Lee, C.-W.; Liang, Y.-R.; Lee, G.-H.; Peng, S.-M.; Yeh, C.-Y. *Tetrahedron Lett.* **2008**, *49*, 7223.
21. Murashima, T.; Uchihara, Y.; Wakamori, N.; Uno, H.; Ogawa, T.; Ono, N. *Tetrahedron Lett.* **1996**, *37*, 3133.
22. These results were presented, in part, at the following meetings: (a) Smith, B.E.; Lash, T.D. *Book of Abstracts* 233rd National American Chemical Society Meeting, Chicago, Illinois, March 2007; CHED 736. (b) Smith, B.E.; Lash, T.D. *Book of Abstracts* 235th National Meeting of the American Chemical Society, New Orleans, Louisiana, April 2008, ORGN 377.
23. Shvedov, V. I.; Altukhova, L. P.; Grinev, A. N. *Khim. Geterotsikl. Soedin.* **1972**, 342.
24. (a) Rexhausen, H.; Gossauer, A. *J. Chem. Soc., Chem. Commun.* **1983**, 275; (b) Gossauer, A. *Bull. Soc. Chim. Belg.* **1983**, *92*, 793.
25. (a) Arsenault, G. P.; Bullock, E.; MacDonald, S. F. *J. Am. Chem. Soc.* **1960**, *82*, 4384; (b) Cavaleiro, J. A. S.; Rocha Gonsalves, A. M. d'A.; Kenner, G. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1771; (c) Lash, T. D. *Chem.—Eur. J.* **1996**, *2*, 1197.
26. Lash, T. D.; Chaney, S. T.; Richter, D. T. *J. Org. Chem.* **1998**, *63*, 9076.
27. Lash, T. D. *J. Porphyrins Phthalocyanines* **1997**, *1*, 29.
28. Smith, K. M. In *Porphyrins and Metalloporphyrins*; Smith, K. M., Ed.; Elsevier: Amsterdam, 1975; pp 3–28.
29. Medforth, C. J. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic: San Diego, 2000; Vol. 5, pp 1–80.
30. Beresford, G. D.; Stoddart, J. F. *Tetrahedron Lett.* **1980**, *21*, 867.
31. Lash, T. D.; Bellettini, J. R.; Bastian, J. A.; Couch, K. B. *Synthesis* **1994**, 170.
32. Smith, K. M.; Minnetian, O. M. *J. Org. Chem.* **1985**, *50*, 2073.
33. Lash, T. D.; Armiger, Y. L. S.-T.-T. *J. Heterocycl. Chem.* **1991**, *28*, 965.