Pergamon

Tetrahedron 54 (1998) 6299–6310

TETRAHEDRON

Porphyrins with Exocyclic Rings. Part 12.[1] Synthesis of *meso*,β-Butano- and *meso*,β-Pentanoporphyrins from Cycloalka[*b*]pyrroles.[2]

Jolie A. Bastian and Timothy D. Lash*

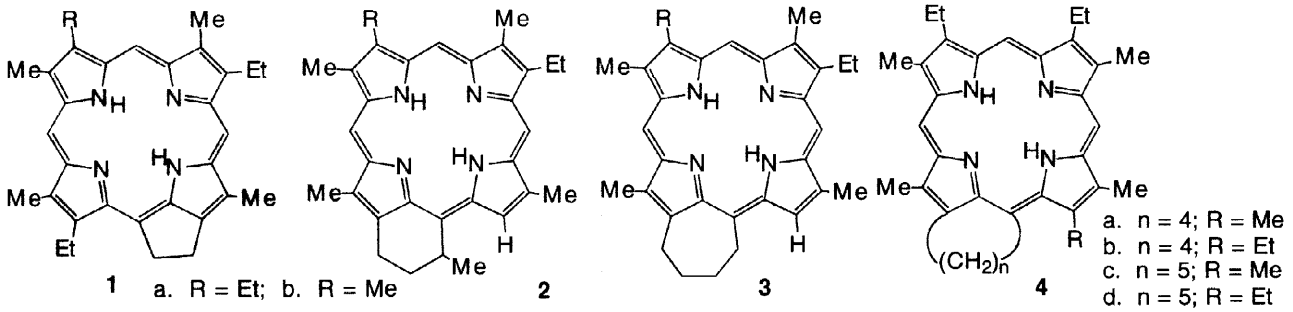
Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160, U.S.A.

Received 18 January 1998; revised 19 March 1998; accepted 23 March 1998

Abstract: *Pyrroles **5** with b-face fused seven- or eight-membered carbocyclic rings were prepared in good yields by Knorr-type condensations with cycloheptanone or cyclooctanone, respectively. Treatment with lead tetraacetate in dichloromethane afforded the labile ω-acetates **8** and subsequent acid catalyzed condensation with α-unsubstituted pyrrole-2-carboxylates yielded the related pyrrolylcycloalka[b]pyrroles **29** and **30**. The α-unsubstituted pyrroles **14** and **23** were prepared by condensing α,β-unsubstituted ketones, or their β-acetoxycarbonyl precursors, with benzyl N-tosylglycinate in the presence of DBU, followed by dehydration with $POCl_3$-pyridine and base catalyzed elimination of p-toluenesulfinic acid. Dipyrrole dibenzyl esters **29** and **30** were hydrogenolysed over 10% Pd-C to give the corresponding dicarboxylic acids. Acid catalyzed condensation with diformyldipyrrylmethane **33** under modified MacDonald "2 + 2" conditions afforded a series of four cycloalkanoporphyrins **4a-d** with seven- or eight-membered exocyclic rings. Although the meso,β-butanoporphyrins **4a** and **4b** were isolated in good yields, poorer results were obtained for the related meso,β-pentanoporphyrins **4c** and **4d**. It is proposed that the eight-membered carbocyclic ring distorts the geometry of the open-chain tetrapyrrolic intermediates and this deleterious influence results in the lower yields observed.* © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Porphyrins with exocyclic rings (e.g. **1-3**) are commonly found as their nickel(II) or vanadyl chelates in organic-rich sedimentary materials such as oil shales and petroleum.[3] Although the synthesis of deoxophyllo-erythroetioporphyrin (**1a**) a commonly occurring sedimentary porphyrin, has been investigated over a considerable number of years,[4] albeit with limited success, porphyrins with larger fused ring systems have received little attention. In other laboratories, carbocyclic rings have been built onto preformed porphyrin structures.[5] Although this strategy has some advantages, most of the new chemistry involved takes place in the later stages of the synthesis and multiple synthetic steps on limited quantities of porphyrin precursors are necessary. We have been interested in the synthesis of cycloalkanoporphyrins (CAPs) for many years in relation to investigations into the origins and spectroscopic characterization of these unusual porphyrin structures.[6-10] In



1 a. R = Et; b. R = Me 2 3 4

* E-mail: tdlash@rs6000.cmp.ilstu.edu Fax: (309) 438-5538

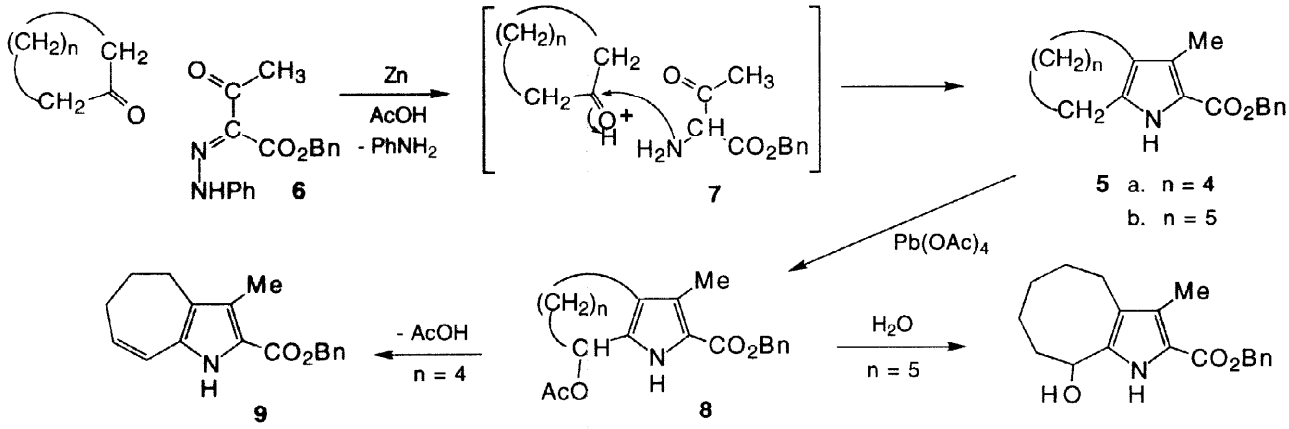
PII: S0040-4020(98)00327-5

our studies, we have elected to start out with the carbocyclic rings in the form of a cyclic ketone, and effectively build the porphyrin onto this structural unit. In so doing, much of the synthetic methodology is developed at an early stage in the synthesis, and the chemistry of biologically active cycloalkanopyrroles can also be explored.[11] In earlier papers in this series, full details on the synthesis of porphyrins with five- or six- membered exocyclic rings have been reported.[9,10] In this report, the synthesis of porphyrins with seven or eight-membered rings (**4a-d**) are detailed and alternative routes to dialkylpyrrole precursors are disclosed.

RESULTS AND DISCUSSION

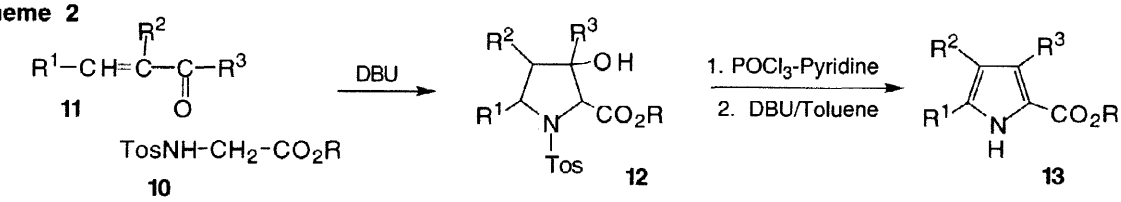
The synthesis of porphyrins with medium sized carbocyclic rings relies on the availability of suitably substituted cycloalkanopyrroles **5** (Scheme 1). These were prepared by condensing cycloheptanone or cyclooctanone with phenylhydrazone **6** in the presence of zinc dust in buffered acetic acid to give the corresponding bicyclic pyrroles. The zinc reductively cleaves aniline from **6** to generate the aminoketone **7** and subsequent nucleophilic attack onto the cyclic ketone, followed by elimination of water and cyclization of the intermediary enamine leads to the desired pyrrolic products. Initially these reactions were carried out at moderate temperatures (80-90°C), in accord with the literature for Knorr pyrrole-type condensations, but this gave the required products in modest yields (20-25%). After much trial and error, we found that much higher reaction temperatures were beneficial (130°C) and this allowed these important intermediates to be obtained in substantially improved yields (50-62%).

Scheme 1



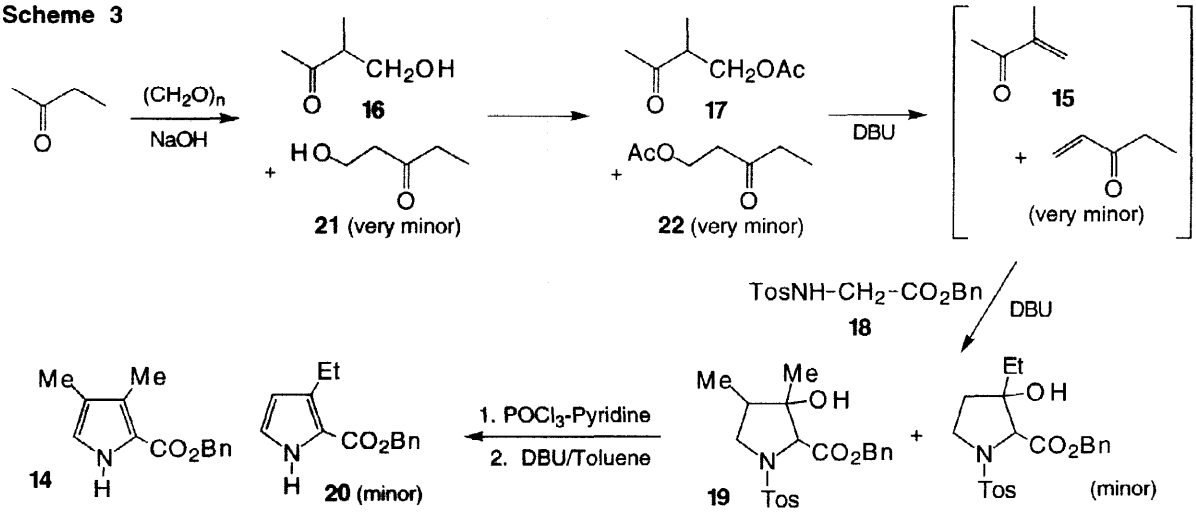
We have previously demonstrated that *b*-cycloalkenopyrroles react regioselectively with lead tetraacetate at the α-CH_2 unit to give the related ω-acetate derivatives (i.e., structure **8**). The seven-membered ring system **5a** reacted with lead tetraacetate in acetic acid to give the vinylic structure **9**, in accord with our previous observations for *b*-cycloheptenopyrroles,[8a] but the required acetate **8a** could be obtained in excellent yields when dichloromethane was used as the reaction solvent. In acetic acid, **8a** is undoubtedly formed as an intermediate but it is so prone to elimination under mildly acidic conditions that the unsaturated structure **9** forms spontaneously. This was not a problem for the reaction of lead tetraacetate with *b*-cyclooctenopyrrole **5b**, although the resulting acetoxy derivative had a tendency to undergo hydrolysis to the corresponding alcohol when the conventional solvent, acetic acid, was used. Hence, dichloromethane was the solvent of choice in this case as well. The acetates **8a** and **8b** were fully characterized, although for preparative studies it was more convenient to use the crude product without purification.

Scheme 2



In order to elaborate these cycloalkanopyrroles to give the necessary dipyrrolic intermediates for our syntheses, two benzyl 5-unsubstituted pyrrole-2-carboxylates were required. Although several routes to structures of this type have been described,[12,13] we were interested in developing an alternative approach to these valuable synthetic intermediates. N-Tosylglycinate esters **10** have been shown to condense with certain α,β-unsaturated ketones **11** in the presence of an alkoxide base to give hydroxypyrrolidines **12**.[14] Dehydration with $POCl_3$ and pyridine affords the corresponding 2- or 3-pyrrolines (the regiochemistry appears to vary depending on the substituents present) and further base catalyzed elimination gives the pyrrole-2-carboxylates **13**.[14,15] We have shown that the use of the non-nucleophilic base DBU in place of potassium *tert*-butoxide in the first and third steps substantially improves the yields of pyrrole products and allows the chemistry to be extended so that α,β-unsaturated aldehydes can be utilized as well.[15] In the earlier study, pyrroles with a single alkyl substituent at positions 3, 4 or 5 were prepared; this approach was least effective when a 5-alkyl substituent was introduced (i.e., for R^1 = Me or Et) and ketones still afforded much better yields than aldehydes.[15] We speculated that this methodology might be applicable to the synthesis of the required 5-unsubstituted 3,4-dialkylpyrroles **13**, i.e. where R^1 = H and R^2,R^3 = alkyl. However the α,β-unsaturated ketones needed for this work were not commercially available and it was necessary to generate these compounds by the chemistry described below.

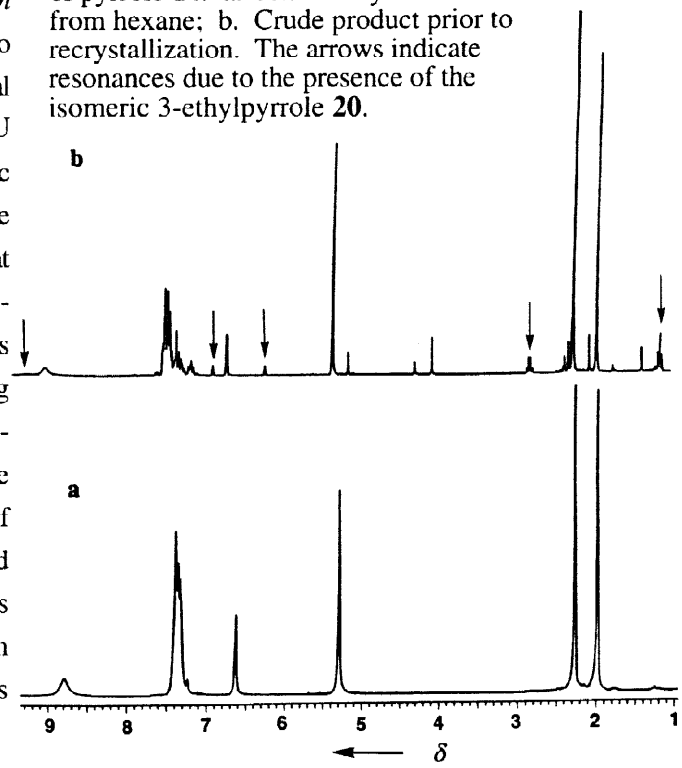
Scheme 3



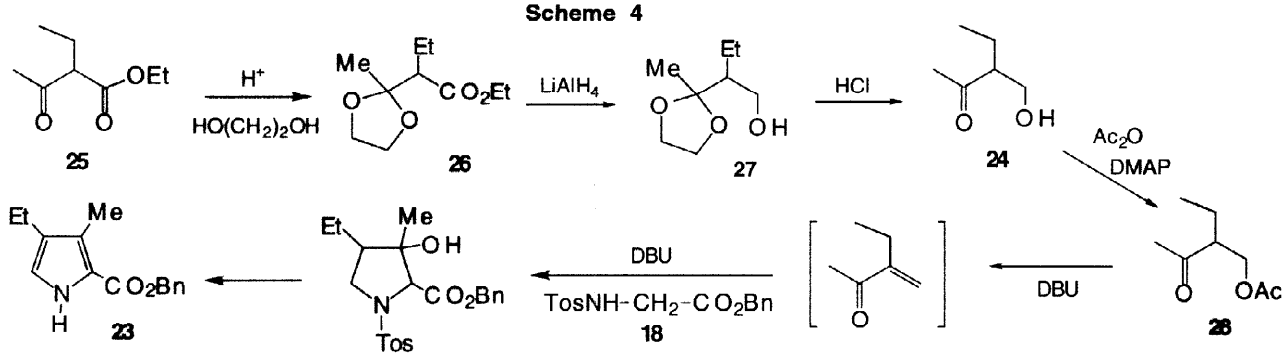
Benzyl 3,4-dimethylpyrrole-2-carboxylate (**14**) was prepared from 3-methyl-3-buten-2-one (**15**; Scheme 3). Methyl ethyl ketone was condensed with paraformaldehyde in the presence of sodium hydroxide to give **16**[16] and subsequent acylation with acetic anhydride and DMAP afforded the acetate **17**. Initially, **17** was eliminated by treatment with iodine[17] to give the α,β-unsaturated ketone **15** and condensed with benzyl N-tosylglycinate (**18**) in the presence of 1 equivalent of DBU to give the hydroxypyrrolidine **19**. Subsequently, it

was found to be far more convenient to condense **17** with **18** using excess DBU; **15** is thereby generated *in situ* and further reacts to form the pyrrolidine **19**. No attempt was made to purify **19**, and the crude material was treated with $POCl_3$-pyridine (dehydration) and DBU in refluxing toluene (elimination of *p*-toluenesulfinic acid) to give the required dimethylpyrrole **14**. The proton NMR spectrum for the crude product showed that **14** was contaminated with a small amount of benzyl 3-ethylpyrrole-2-carboxylate (**20**) (Figure 1). This impurity was due to the hydroxyketone **16** being contaminated with a small amount of 1-hydroxy-3-pentanone (**21**) (i.e. the first step falls short of complete regioselectivity). Hence, **15** contains a small amount of acetate **22** and further reaction leads to the observed pyrrole contaminant. Fortunately, this biproduct was easily removed by recrystallizing the crude product from hexane. Pure pyrrole **14** was obtained as white crystals in 30% yield from the β-acetoxyketone **17**.

Figure 1: 300 MHz proton NMR spectra of pyrrole **14**: a. After recrystallization from hexane; b. Crude product prior to recrystallization. The arrows indicate resonances due to the presence of the isomeric 3-ethylpyrrole **20**.

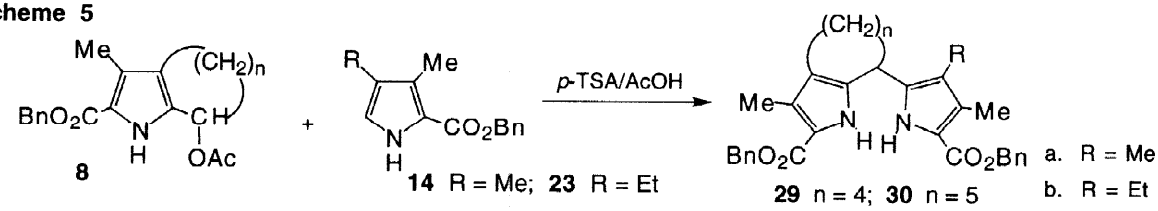


Scheme 4



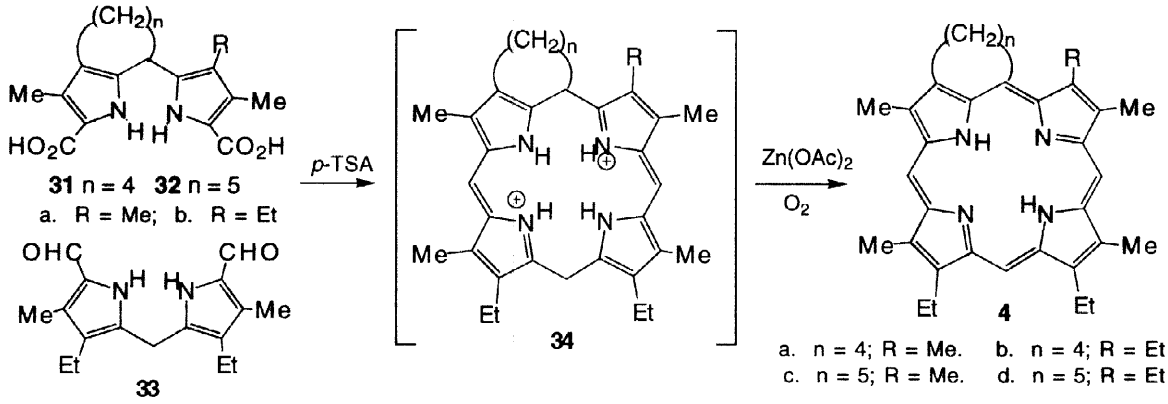
The same approach was also applied to the preparation of benzyl 4-ethyl-3-methylpyrrole-2-carboxylate (**23**; Scheme 4). However, in order to avoid the formation of isomeric biproducts, β-hydroxyketone **24** was generated in a slightly different fashion. Ethyl 3-ethylacetoacetate (**25**)[18] was protected with ethylene glycol as the ketal **26** and reduced with lithium aluminum hydride to give the alcohol **27**. Deprotection with hydrochloric acid in ethanol-water then gave the required hydroxyketone **24**. This was converted to the corresponding acetate **28** and taken on to pyrrole **23** by the procedures described above (Scheme 4). Pyrrole **23** was obtained in reasonable yield as a pale yellow oil; however, careful chromatography was required to purify the product. Subsequent to this study we developed an alternative strategy for the synthesis of benzyl 5-unsubstituted pyrrole-2-carboxylates using benzyl isocyanoacetate[19] and this method commonly provides a more convenient route to the one described here. However, these results demonstrate that the N-tosylglycinate approach is fairly general and hence may have applications where the isocyanate methodology is unsuccessful.

Scheme 5



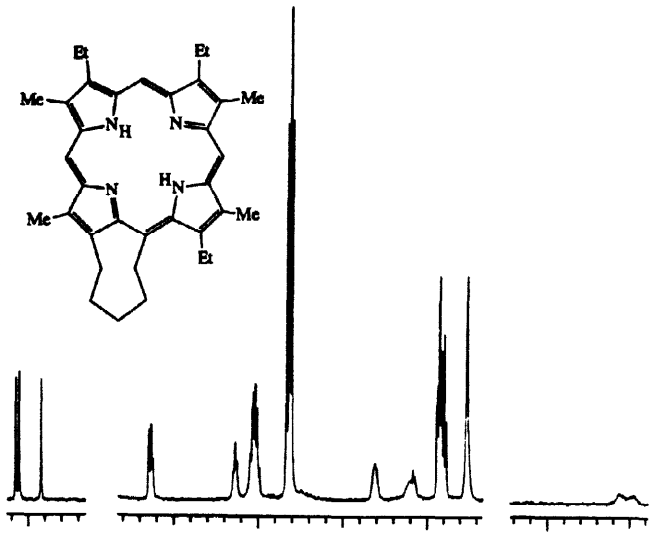
Now that α-free pyrroles **14** and **23** were available, the pivotal dipyrrolic intermediates **29** and **30** could be prepared (Scheme 5). Condensation of **8a** or **8b** with these α-unsubstituted pyrroles and *p*-toluenesulfonic acid in acetic acid gave the pyrrolylcycloalkenopyrroles **29a,b** and **30a,b**, respectively, in 56-90% yield. Hydrogenolysis of the benzyl esters over 10% palladium-charcoal afforded the related dicarboxylic acids **31** and **32** in excellent yields (Scheme 6). The four dipyrrolic dicarboxylic acids were individually condensed with diformyldipyrrylmethane **33** in the presence of *p*-toluenesulfonic acid in methanol-dichloromethane (the MacDonald condensation[20]). The intermediary porphodimethenes **34** were treated with saturated zinc acetate in methanol and allowed to air oxidize over a period of 2 days at room temperature.[9,10] Following demetallation, the crude product was purified by column chromatography and recrystallized from chloroform-methanol. The seven-membered ring porphyrins **4a** and **4b** were thereby obtained in good yields (23-26%) and these results compare favorably to those previously obtained for porphyrins with six-membered exocyclic rings. However, the yields of porphyrins **4c** and **4d**, obtained from the condensation of dipyrroles **32a,b**, which contain eight-membered carbocyclic rings, with dialdehyde **33** were significantly reduced (12-16%) indicating that the eight-membered ring has a substantial deleterious influence on porphyrin formation. In the absence of carbocyclic rings, open chain tetrapyrrolic structures have a tendancy to take on a helical arrangement that brings the two terminal pyrrole units into close proximity so that cyclization reactions can occur. We speculate that the preferred conformation of the eight-membered ring system induces the two terminal pyrrole units of the putative tetrapyrrolic intermediate (**35** or its regioisomer) to twist away from one another making it more difficult for macrocyclic cyclization to occur. In this chemistry, six- and seven-membered rings do not appear to significantly interfer with porphyrin formation, and the steric and/or conformational requirements of these carbocyclic rings must be compatible with the required geometry of the intermediary tetrapyrrolic species.

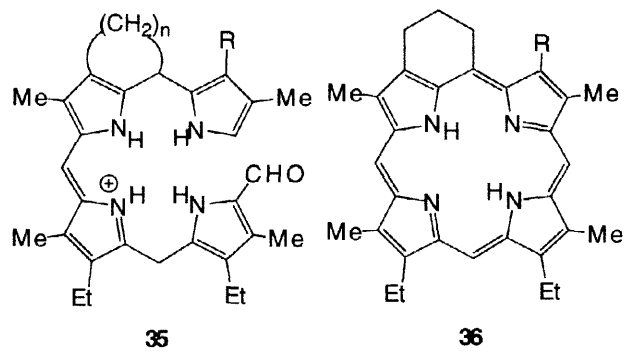
Scheme 6



The structures of porphyrins **4a-d** were confirmed by NMR spectroscopy (e.g. Fig. 2) and mass spectrometry. The proton NMR data demonstrated the presence of the usual strong porphyrin diatropic ring currents and the *meso*-protons were observed as three singlets in each case near 10 ppm. The *meso*-CH_2 of the carbocycle was deshielded to 4.8 ppm in **4a** and **4b**, but the equivalent units shifted downfield to 5.3 ppm in the eight-membered ring systems. The β-CH_2 moieties of the eight-membered rings in **4c** and **4d** were also significantly deshielded compared to their seven-membered ring counterparts (*meso*,β-propanoporphyrins **36** gave[10] values closer to those observed for **4c** and **4d**), although the resonances for the various methyl and ethyl substituents were similar for both the butano- and pentanoporphyrins. These differences in the spectroscopic data may be due to the seven-membered rings geometry which allows the ring methylenes to lie closer to the plane of the porphyrin macrocycle, although steric interactions in the crowded eight-membered ring system may also be a factor. The uv-vis spectra for **4a-d** in dichloromethane showed the expected strong Soret bands at 404 nm and phyllo-type Q band regions (IV > II > III > I), and in this respect these porphyrins were virtually indistinguishable from their previously synthesized ring homologs **36**.[10]

Figure 2: 300 MHz proton NMR spectrum of *meso*,β-Pentanoporphyrin **4d** in $CDCl_3$.





CONCLUSIONS

Cycloheptanone and cyclooctanone condense with phenylhydrazone **6** in the presence of zinc dust and acetic acid at 130°C to give *b*-cycloalkenopyrroles **5** in good yields and subsequent reaction with lead tetraacetate in dichloromethane affords the corresponding ω-acetates **8**. Acid catalyzed condensation with benzyl 5-unsubstituted pyrrole-2-carboxylates, which may be prepared from α,β-unsaturated ketones or their β-acetoxyketone precursors, and benzyl N-tosylglycinate gave a series of dipyrroles that incorporate 7- or 8-membered carbocycles in excellent yields. Hydrogenolysis of the benzyl ester protective groups, followed by acid catalyzed "2 + 2" MacDonald condensation with a dipyrrylmethanedialdehyde gave four examples of porphyrins with fused seven- or eight-membered exocyclic rings. Although the seven-membered ring porphyrins were isolated in good yields, somewhat poorer results were obtained for the eight-membered ring system. Nevertheless, this approach allows straightforward access to these cycloalkanoporphyrins, which are valuable standards for ongoing geochemical and spectroscopic studies.[21]

EXPERIMENTAL

Hydrogenations were carried out using a Parr hydrogenator at 30-40 psi. Chromatography was performed using Grade 3 neutral alumina or 70-230 mesh silica gel. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 710B spectrometer or a Perkin-Elmer 1600 Series FT-IR Spectrometer. UV spectra were obtained on a Beckmann DU-40 spectrophotometer. NMR spectra were recorded on a Hitachi-Perkin Elmer R24B 60 MHz nmr spectrometer or a Varian Gemini-300 nmr spectrometer; partial funding for two 300 MHz NMR spectrometers was provided by the National Science Foundation under Grant Numbers CHE-9001175 and DUE-9452437. Mass spectral determinations were made at the Midwest Center for Mass Spectrometry at the University of Nebraska-Lincoln with partial support by the National Science Foundation, Biology Division (Grant No. DIR9017262), or the Mass Spectral Laboratory, School of Chemical Sciences, University of Illinois at Urbana-Champaign, supported in part by a grant from the National Institute of General Medical Sciences (GM 27029). Elemental analyses were obtained from Micro-Analysis, Inc., Wilmington, DE 19808, or the School of Chemical Sciences Microanalysis Laboratory at the University of Illinois.

Benzyl 3-Methylcyclohepta[*b*]pyrrole-2-carboxylate (**5a**) (with T.H. Nguyen): Cycloheptanone (7.00 g) and anhydrous sodium acetate (6.25 g) were dissolved in glacial acetic acid (75 mL) and heated to 130°C. A mixture of benzyl 2,3-dioxobutanoate-2-phenylhydrazone[10] (**6**; 18.50 g) and zinc dust (18.75 g) was added slowly in portions to the solution maintaining the temperature at 130°C. When the addition was complete, it was stirred for an additional 1 h at 130°C. The solution was cooled to 70°C and decanted into an ice-water slurry. The residual zinc was washed several times with hot glacial acetic acid, which was combined with the ice-water solution. The mixture was allowed to stand overnight. The resulting precipitate was filtered and washed several times with water to remove traces of acetic acid. Recrystallization from ethanol gave the title compound (9.143 g; 52%) as white crystals, mp 132.5-134°C; IR (nujol mull): ν 3298 (NH str.), 1659 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.64 (4H, m), 1.81 (2H, m) (3 x CH_2), 2.27 (3H, s, pyrrole-CH_3), 2.47 (2H, t, 4-CH_2), 2.63 (2H, t, 8-CH_2), 5.28 (2H, s, CH_2Ph), 7.33-7.38 (5H, m, Ph), 8.70 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 10.57, 25.08, 27.48, 28.81, 29.42, 32.16, 65.49, 115.39, 124.42, 127.76, 128.25, 128.34, 128.80, 137.15, 161.78. Anal. calc. for $C_{18}H_{21}NO_2$: C, 76.28; H, 7.48; N, 4.94. Found: C, 76.24; H, 7.29; N, 4.95.

Benzyl 3-Methylcycloocta[*b*]pyrrole-2-carboxylate (**5b**) (with J. Mannin): Prepared by the procedure detailed above from cyclooctanone (6.30 g) and phenylhydrazone **6**[10] (14.80 g), maintaining the reaction temperature at 120-130°C throughout. Recrystallization from 95% ethanol gave the cycloocta[*b*]pyrrole (8.44-9.34 g; 57-63%) as long white needles, mp 135-137°C. An analytical sample was obtained by recrystallization from hexane as white crystals, mp 137°C; IR (nujol mull): ν 3289 (NH str.), 1659 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.39 (4H, m), 1.58 (4H, m) (4 x CH_2), 2.27 (3H, s, pyrrole-CH_3), 2.50 (2H, t, 4-CH_2), 2.64 (2H, t, 9-CH_2), 5.29 (2H, s, CH_2Ph), 7.31-7.43 (5H, m, Ph), 8.86 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 10.41, 21.94, 25.58, 25.67, 25.93, 29.48, 29.92, 65.30, 116.08, 121.75, 127.91, 128.01, 128.45, 135.27, 136.76, 161.56. Anal. calc. for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.79; N, 4.71. Found: C, 76.83; H, 7.63; N, 4.65.

Benzyl 8-Acetoxy-3-methylcyclohepta[*b*]pyrrole-2-carboxylate (**8a**): Lead tetraacetate (1.05 equiv; 0.82 g) was added to a stirred solution of benzyl 3-methylcyclohepta[*b*]pyrrole-2-carboxylate (0.50 g) in dichloromethane (10 mL) and the resulting mixture was allowed to stir at room temperature for 3 h. The mixture was washed with water and 5% aqueous sodium bicarbonate solution, dried over sodium sulfate and evaporated under reduced pressure to give a pale yellow oil. Crystallization from dichloromethane-hexane gave the title acetate (0.32 g; 53%) as off-white crystals, mp 86-89°C. Further recrystallization from hexane gave an analytically pure sample as white crystals, mp 94-95°C; IR (nujol mull): ν 3309 (NH str.), 1733, 1654 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.65 (1H, m), 1.80-2.05 (5H, m) (3 x CH_2), 2.07 (3H, s, $OCOCH_3$), 2.25 (3H, s, pyrrole-CH_3), 2.53 (2H, t, 4-CH_2), 5.24-5.36 (2H, AB q, CH_2Ph), 5.82-5.85 (1H, dd, CHOAc), 7.31-7.43 (5H, m, Ph), 8.89 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 10.41, 21.30, 24.39, 25.22, 28.15, 32.29, 65.76, 70.09, 117.39, 124.88, 127.05, 128.34, 128.39, 128.84, 132.58, 136.93, 161.60, 171.17. Anal. calc. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.64; H, 6.81; N, 4.10.

Benzyl 9-Acetoxy-3-methylcycloocta[*b*]pyrrole-2-carboxylate (**8b**): Lead tetraacetate (1.05 equiv; 0.785 g) was added to a stirred solution of benzyl 3-methylcycloocta[*b*]pyrrole-2-carboxylate (0.50 g) in dichloromethane (10 mL) and the resulting mixture was allowed to stir at room temperature for 16 h. The mixture was washed with water and 5% aqueous sodium bicarbonate solution, dried over sodium sulfate and evaporated under reduced pressure to give the required acetate (0.60 g; quantitative) as a pale yellow oil (>95% pure by NMR). Attempts to crystallize this compound were unsuccessful; IR (neat): ν 3308 (NH str.), 1736, 1687 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.3-1.86 (7H, m), 1.99-2.07 (1H, m) (4 x CH_2), 2.11 (3H, s, $OCOCH_3$), 2.26 (3H, s, pyrrole-CH_3), 2.44-2.54 (1H, m), 2.64-2.74 (1H, m) (4-CH_2), 5.32 (2H, s, CH_2Ph), 5.82-5.98 (1H, dd, CHOAc), 7.30-7.44 (5H, m, Ph),

8.90 (1H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 10.18, 21.29, 21.88, 22.92, 25.21, 29.15, 35.05, 65.79, 70.20118.04, 121.54, 126.98, 128.36, 128.38, 128.84, 132.32, 136.94, 161.87, 170.49.

Benzyl 3,4-dimethylpyrrole-2-carboxylate (**14**):

*4-Hydroxy-3-methyl-2-butanone (**16**):*[16] Ethyl methyl ketone (450 mL) and paraformaldehyde (30.0 g) were stirred at 40°C, and a mixed indicator (1:1 phenol red and bromothymol blue) was added until the solution became pale yellow in color. Aqueous sodium hydroxide solution (1.0 M) was slowly added dropwise until the upper layer was turned blue (when stirring the mixture appears to be purple). After approximately 40 min, all the solid paraformaldehyde had disappeared, and 2 layers were prominent. Glacial acetic acid was added dropwise to neutralize the solution so that there was just enough acid for the mixture to regain its yellow color. After dilution with chloroform, the solution was washed with brine and separated. The organic layer was dried over sodium sulfate, evaporated under reduced pressure, and distilled under reduced pressure to give the ketone as a yellow oil (41.87 g; 41%), bp 90-110°C at 12 mmHg; ^1H NMR ($CDCl_3$): δ 1.12 (3H, d, $CHCH_3$), 2.20 (3H, s, $COCH_3$), 2.73-2.79 (1H, m, CH), 3.39 (1H, br, OH), 3.63-3.78 (2H, m, CH_2OH).

*4-Acetoxy-3-methyl-2-butanone (**17**):* The foregoing hydroxyketone **16** (44.46 g), acetic anhydride (184 mL), dimethylaminopyridine (DMAP; 3.85 g), and chloroform (192 mL) were stirred overnight at room temperature. Methanol (276 mL) was added dropwise while keeping the exothermic reaction under control with an ice bath. After stirring for 30 min, the solution was poured into saturated aqueous sodium bicarbonate (300 mL) in a 2 L separatory funnel (vigorous reaction). Upon extraction with dichloromethane, the organic layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure to give the title compound as a yellow oil (57.5 g; 92%). ^1H NMR ($CDCl_3$): δ 1.15 (3H, d, $CHCH_3$), 2.05 (3H, s, $COCH_3$), 2.22 (3H, s, acetoxy-CH_3), 2.7-3.1 (1H, m, CHCO), 4.11-4.27 (2H, m, CH_2OAc).

*Benzyl 3-Hydroxy-3,4-dimethyl-N-p-toluenesulfonylpyrrolidine-2-carboxylate (**19**):* 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU; 3 equiv; 17.2 g) was added to a stirred solution of **17** (5.42 g) and benzyl N-*p*-toluenesulfonylglycinate (**18**; 12.0 g) in THF (55 mL). The mixture, which turned dark brown, was stirred overnight at room temperature. After dilution with chloroform, the solution was washed with 5% hydrochloric acid, 5% sodium bicarbonate solution, and water. The organic layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure to give the crude pyrrolidine as a dark red-brown oil (14.36 g; 95%).

Benzyl 3,4-dimethylpyrrole-2-carboxylate: Pyrrolidine **19** (14.23 g) was dissolved in pyridine (117 mL). Phosphorus oxychloride (15.3 mL) was added over approximately 10 min, and the resulting mixture was stirred at room temperature overnight. The mixture was poured over ice (approximately 400 mL) and extracted twice with diethyl ether. The combined ethereal layers were washed sequentially with 5% hydrochloric acid, 5% sodium bicarbonate solution, and water. Then, it was dried over sodium sulfate, filtered, and evaporated under reduced pressure to give the intermediary pyrroline as a brown oil (11.0 g; 81%). The crude pyrroline (11.0 g) was dissolved in toluene (59 mL), DBU (2 equiv; 8.71 g) was added over several min and the resulting solution was stirred under reflux overnight. After cooling to room temperature, the solution was diluted with chloroform, and washed successively with 10% hydrochloric acid, 5% sodium bicarbonate solution, and water. The organic layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure to give a brown oil. Chromatography on a silica column, eluting with toluene, and recrystallization from hexane gave the title pyrrole (2.53 g, 39%) as white crystals, mp 73-74°C (lit. mp[13a] 73-75°C); IR (nujol mull): ν 3319 (NH str.), 1669 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.99 (3H, s, 4-CH_3), 2.28 (3H, s, 3-CH_3), 5.29 (2H, s, CH_2Ph), 6.61 (1H, d, pyrrole-H), 7.30-7.41 (5H, m, Ph), 8.85 (1H, br s, NH).

Benzyl 4-Ethyl-3-methylpyrrole-2-carboxylate:

*2-Ethoxycarbonylmethyl-2-methyl-1,3-dioxolane (**26**):* Ethyl 2-ethylacetoacetate[18] (197 g), ethylene glycol (105 g), and toluene (395 mL) were refluxed with *p*-toluenesulfonic acid (47 mg) under a Dean and Stark apparatus until no more water azeotroped over (approx. 19 mL were collected over 3.5 h). The mixture was washed with saturated sodium bicarbonate solution, then saturated sodium chloride solution, dried over sodium sulfate, filtered, and evaporated under reduced pressure. The flask was packed with glass wool to reduce foaming, and the crude product was distilled to give the desired ketal as a pale yellow oil (176.4 g; 70%), bp 210-220°C (lit. bp[17] 100-110°C at 11 mmHg); ^1H NMR ($CDCl_3$): δ 0.88 (3H, t, $CHCH_2CH_3$), 1.25 (3H, t, OCH_2CH_3), 1.37 (3H, s, CH_3), 1.4-1.9 (2H, m, $CHCH_2CH_3$), 2.6 (1H, m, CHCO), 3.92 (4H, br s, $O(CH_2)_2O$), 4.14 (2H, q, OCH_2CH_3).

*2-Hydroxymethyl-2-methyl-1,3-dioxolane **27**:* The foregoing ketal (70.0 g) in ether (20 mL) was added dropwise over 1 h to a mixture of lithium aluminum hydride (9.00 g) and anhydrous ether (165 mL). The resulting mixture was stirred under refluxed for 2 h. After cooling the reaction vessel in ice, water (125 mL) was added cautiously (vigorous reaction) to decompose the residual $LiAlH_4$. The inorganic solids were filtered off, and organic phase was separated. The water layer was extracted with ether, and the

combined ether layers were washed with water, dried over sodium sulfate, and evaporated under reduced pressure. The residual oil was distilled to give the alcohol (40.39 g; 73%) as a colorless oil, bp 131-140°C at 15 mmHg (lit. bp[17] 98-102°C at 12 mmHg); ^{1}H NMR ($CDCl_3$): δ 1.00 (3H, t, CH_2CH_3), 1.28 (3H, s, CH_3), 1.3-1.9 (3H, m, $CHCH_2CH_3$), 3.17 (1H, s, OH), 3.63 (2H, d, CH_2OH), 3.95 (4H, br s, $O(CH_2)_2O$).

3-Ethyl-4-hydroxy-2-butanone (24): Hydroxyketal **27** (20.0 g) was heated with water (50 mL), ethanol (4.7 mL), and 1 drop of concentrated hydrochloric acid for 90 min in a boiling water bath. After neutralization with dilute sodium hydroxide (in a separatory funnel), the solution was saturated with ammonium sulfate and extracted with ether. The layers were separated, and the aqueous layer was reextracted with ether. The combined etherial layers were dried over sodium sulfate, filtered, evaporated under reduced pressure, and distilled *in vacuo* to give the hydroxyketone (10.1 g; 69%) as a colorless oil, bp 120-132°C at 28 mmHg (lit. bp[17] 91-94°C at 12 mmHg). ^{1}H NMR ($CDCl_3$): δ 0.90 (3H, t, CH_2CH_3), 1.52 (2H, m, CH_2CH_3), 2.19 (3H, s, $COCH_3$), 2.63 (1H, m, CHCO), 3.1 (1H, br, OH), 3.68 (2H, br d, CH_2OH).

4-Acetoxy-3-ethyl-2-butanone (28): Prepared from the foregoing ketoalcohol (18.31 g) from the procedure described above as detailed for **17**. The crude acetoxy compound was obtained as a yellow oil (20.0 g; 80%); ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, t, CH_2CH_3), 1.5-1.7 (2H, m, CH_2CH_3), 2.04 (3H, s, $COCH_3$), 2.21 (3H, s, acetoxy-CH_3), 2.76-2.80 (1H, m, CH), 4.21 (2H, d, CH_2OAc).

Benzyl 3-Hydroxy-4-ethyl-3-methyl-N-p-toluenesulfonylpyrrolidine-2-carboxylate: DBU (57.8 g) was added to a stirred solution of **28** (20.00 g) and benzyl N-*p*-toluenesulfonylglycinate (**18**; 40.40 g) in THF (176 mL). The mixture, which turned dark brown, was stirred overnight at room temperature. After dilution with chloroform, the solution was washed with 5% hydrochloric acid, 5% sodium bicarbonate solution, and water. The organic layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure to give the crude pyrrolidine as a dark red-brown oil (50.14 g; 95%).

Benzyl 4-ethyl-3-methylpyrrole-2-carboxylate:[13b,19] The foregoing pyrrolidine (12.06g) was converted to the corresponding pyrroline (brown oil; 9.41 g; 82%) by the procedure described above for **19**. The crude pyrroline (9.41 g) was treated with DBU as described for pyrrole **14**, and the resulting product purified by column chromatography on silica gel, eluting with toluene. The title pyrrole was isolated as a pale yellow oil (1.856 g; 32%). ^{1}H NMR ($CDCl_3$): δ 1.15 (3H, t, CH_2CH_3) 2.29 (3H, s, pyrrole-CH_3), 2.42 (2H, q, CH_2CH_3), 5.39 (2H, s, CH_2Ph), 6.65 (1H, d, pyrrole-H), 7.31-7.42 (5H, m, Ph), 8.91 (1H, br s, NH).

Benzyl 8-(5-Benzyloxycarbonyl-3,4-dimethyl-2-pyrrolyl)-3-methylcyclohepta[*b*]pyrrole-2-carboxylate (**29a**): Lead tetraacetate (1.05 equiv; 4.93 g) was added in portions over several minutes to a stirred solution of benzyl 3-methylcyclohepta[*b*]pyrrole-2-carboxylate (3.00 g) in dichloromethane (60 mL) and the resulting mixture was allowed to stir for 3 h. The mixture was washed with water and 5% aqueous sodium bicarbonate solution, dried over sodium sulfate and evaporated under reduced pressure to give the acetoxy compound as a pale yellow oil. The crude acetate and benzyl 3,4-dimethylpyrrole-2-carboxylate (2.183 g; 0.9 equivalents) were dissolved in glacial acetic acid (60 mL), *p*-toluenesulfonic acid (116 mg) was added and the mixture stirred at room temperature for 2 h. The solution was poured into an ice/water slurry (600 mL) and allowed to stand for 1 h. The mixture was extracted with ether (3 x 150 mL) and the combined organic layers were washed with saturated sodium bicarbonate solution (150 mL) and water (150 mL). The etherial layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica, eluting with dichloromethane. Recrystallization from ethanol gave the desired dipyrrole (3.804 g; 78%) as white crystals, mp 129-130°C. IR (nujol mull): ν 3289 (NH str.), 1679 (C=O str.), 1661 (C=O str.) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.55-1.9 (4H, m), 1.98 (2H, m) (-$(CH_2)_3$-), 1.94 (3H, s), 2.27 (6H, s) (3 x pyrrole-CH_3), 2.49 (1H, m), 2.62 (1H, m) (pyrrole-CH_2), 4.13 (1H, m, bridge-CH), 5.22 (2H, s), 5.26 (2H, s) (2 x CH_2Ph), 7.3-7.4 (10H, m, 2 x Ph), 8.43 (1H, br s), 8.81 (1H, br s) (2 x NH); ^{13}C NMR ($CDCl_3$): δ 9.00, 10.55, 10.71, 24.81, 28.09, 29.64, 33.46, 37.79, 65.35, 65.55, 116.10, 117.01, 117.50, 123.50, 127.27, 127.75, 127.91, 128.47, 133.30, 135.19, 136.47, 136.56, 161.24, 161.40. Anal. calc. for $C_{32}H_{34}N_2O_4$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.15; H, 6.74; N, 5.42.

Benzyl 8-(5-Benzyloxycarbonyl-4-ethyl-3-methyl-2-pyrrolyl)-3-methylcyclohepta[*b*]pyrrole-2-carboxylate (**29b**): Prepared from benzyl 3-methylcyclohepta[*b*]pyrrole-2-carboxylate (1.747 g) and benzyl 4-ethyl-3-methylpyrrole-2-carboxylate (1.50 g) by the procedure detailed above. Recrystallization from ethanol afforded the dipyrrole as white crystals (1.794 g; 56%), mp 125.5-126°C. IR (nujol mull): ν 3319 (NH str.), 3256 (NH str.), 1680 (C=O str.), 1660 (C=O str.) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.05 (3H, t, J = 7.5 Hz, CH_2CH_3), 1.5-2.06 (6H, m, -$(CH_2)_3$-), 2.28 (3H, s), 2.32 (3H, s) (2 x pyrrole-CH_3), 2.39 (2H, q, J = 7.5 Hz, CH_2CH_3), 2.52 (1H, m), 2.68 (1H, m) (pyrrole-CH_2CH_2), 4.12 (1H, m, bridge-CH), 5.24 (2H, s), 5.29 (2H, s) (2 x CH_2Ph), 7.3-7.45 (10H, m, 2 x Ph), 8.20 (1H, br s), 8.55 (1H, br s) (2 x NH); ^{13}C NMR ($CDCl_3$): δ 10.51, 10.59, 15.50, 17.32, 24.80, 28.03, 29.80, 34.14,

37.57, 65.32, 65.57, 116.03, 117.86, 123.45, 123.88, 127.26, 127.34, 127.73, 127.96, 128.41, 128.46, 132.82, 135.40, 136.44, 136.44, 136.56, 161.17, 161.35. Anal. calc. for $C_{33}H_{36}N_2O_4$: C, 75.55; H, 6.92; N, 5.34. Found: C, 75.41; H, 6.90; N, 5.31.

Benzyl 9-(5-Benzyloxycarbonyl-3,4-dimethyl-2-pyrrolyl)-3-methylcycloocta[*b*]pyrrole-2-carboxylate (**30a**): Prepared from benzyl 3-methylcycloocta[*b*]pyrrole-2-carboxylate (3.00 g) and benzyl 3,4-dimethylpyrrole-2-carboxylate (2.08 g) as described previously for **29a**. Recrystallization from ethanol afforded the dipyrrole (4.292 g; 90%) as a white powder, mp 131.5-132°C; IR (nujol mull): ν 3395 (NH str.), 3319 (NH str.), 1707 (C=O str.), 1644 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.49 (4H, m), 1.6-2.1 (4H, m) (-$(CH_2)_4$-), 1.78 (3H, s), 2.27 (6H, s), (3 x pyrrole-CH_3), 2.53 (1H, m), 2.74 (1H, m) (pyrrole-CH_2), 4.23 (1H, m, bridge-CH), 5.26 (2H, s), 5.33 (2H, s) (2 x CH_2Ph), 7.3-7.45 (10H, m, 2 x Ph), 8.15 (1H, br s), 8.74 (1H, br s) (2 x NH); ^{13}C NMR ($CDCl_3$): δ 8.78, 10.33, 10.67, 22.53, 25.34, 25.52, 29.83, 33.71, 34.40, 65.38, 65.58, 117.25, 117.33, 117.55, 121.96, 126.57, 127.94, 128.30, 128.43, 128.49, 128.61, 129.44, 130.79, 161.45, 161.51. Anal. calc. for $C_{33}H_{36}N_2O_4$: C, 75.55; H, 6.92; N, 5.34. Found: C, 75.18; H, 6.80; N, 5.27.

Benzyl 9-(5-Benzyloxycarbonyl-4-ethyl-3-methyl-2-pyrrolyl)-3-methylcycloocta[*b*]pyrrole-2-carboxylate (**30b**): Prepared from benzyl 3-methylcycloocta[*b*]pyrrole-2-carboxylate (1.00 g) and benzyl 4-ethyl-3-methylpyrrole-2-carboxylate (0.736 g) as described previously for **29a**. Recrystallization from ethanol (1.306 g; 72%) afforded the dipyrrole as an off-white solid, mp 134.5-135°C; IR (nujol mull): ν 3367 (NH str.), 3329 (NH str.), 1676 (C=O str.), 1646 (C=O str.) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.87 (3H, t, CH_2CH_3), 1.46 (4H, m), 1.6-1.85 (2H, m), 1.95-2.05 (2H, m) (4 x -$(CH_2)_4$-), 2.28 (3H, s), 2.30 (3H, s) (2 x pyrrole-CH_3), 2.29 (2H, quartet obscured by the foregoing methyl singlets, CH_2CH_3), 2.50 (1H, m), 2.74 (1H, m) (pyrrole-CH_2CH_2), 4.27 (1H, t, bridge CH), 5.25 (2H, s), 5.32 (2H, AB quartet) (2 x CH_2Ph), 7.3-7.45 (10H, m, 2 x Ph), 8.20 (1H, br s), 8.86 (1H, br s) (2 x NH); ^{13}C NMR ($CDCl_3$): δ 10.31, 10.56, 15.00, 17.24, 22.61, 25.37, 25.58, 29.98, 34.02, 34.09, 65.35, 65.61, 117.15, 117.64, 121.88, 124.21, 126.64, 127.70, 127.87, 127.93, 128.39, 128.46, 133.27, 134.40, 136.47, 136.56, 161.39, 161.59. Anal. calc. for $C_{34}H_{38}N_2O_4$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.54; H, 6.99; N, 5.13.

8-(5-Carboxy-3,4-dimethyl-2-pyrrolyl)-3-methylcyclohepta[*b*]pyrrole-2-carboxylic Acid (**31a**): Benzyl 8-(5-benzyloxycarbonyl-3,4-dimethyl-2-pyrrolyl)-3-methylcyclohepta[*b*]pyrrole-2-carboxylate (500 mg) and 10 drops of triethylamine were dissolved in methanol (200 mL) in a hydrogenation vessel, and the solution was purged with nitrogen. Pd/C (10%, 100 mg) was added and the reaction vessel was shaken under an atmosphere of hydrogen at room temperature and 40 psi overnight. The catalyst was filtered off, and the solvent was evaporated under reduced pressure maintaining the temperature below 40°C. The residue was taken up in 5% aqueous ammonia solution, and the catalyst was washed with additional 5% aqueous ammonia to dissolve up any remaining product. The combined ammonia solutions were cooled to 0°C in a ice/salt bath and neutralized to litmus with glacial acetic acid. After standing at 0°C for 1 hr, the precipitate was filtered, washed with liberal amounts of water and dried *in vacuo*. The dicarboxylic acid (289 mg; 89%) was isolated as pale pink crystals, mp 125-126.5°C; ^1H NMR ($CDCl_3$): δ 1.3-2.0 (6H, m, 3 x CH_2), 1.87 (3H, s), 2.20 (3H, s), 2.22 (3H, s) (3 x pyrrole-CH_3), 2.4-2.7 (2H, m, pyrrole-CH_2), 4.17 (1H, m, bridge-CH), 8.7 (1H, br s), 10.0 (1H, br s) (2 x NH). Anal. calc. for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.08; H, 7.03; N, 7.48.

8-(5-Carboxy-4-ethyl-3-methyl-2-pyrrolyl)-3-methylcyclohepta[*b*]pyrrole-2-carboxylic Acid (**31b**): Prepared by the foregoing procedure from benzyl 8-(5-benzyloxy-carbonyl-4-ethyl-3-methyl-2-pyrrolyl)-3-methylcyclohepta[*b*]pyrrole-2-carboxylate (500 mg). The title compound was isolated as a pale orchid solid (300 mg; 91%), mp 135°C, dec; ^1H NMR (d_6-DMSO-$CDCl_3$): δ 0.93 (3H, t, CH_2CH_3), 1.4-1.9 (6H, m, 3 x CH_2), 2.15 (3H, s), 2.20 (3H, s) (2 x CH_3), 2.27 (2H, q, CH_2CH_3), 2.33-2.58 (2H, m, pyrrole-CH_2CH_2), 4.03 (1H, m, bridge-CH), 8.31 (1H, br s), 8.73 (1H, br s) (2 x NH). Anal. calc. for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.43; H, 7.35; N, 8.27.

9-(5-Carboxy-3,4-dimethyl-2-pyrrolyl)-3-methylcycloocta[*b*]pyrrole-2-carboxylic Acid (**32a**): Prepared from benzyl 9-(5-benzyloxycarbonyl-3,4-dimethyl-2-pyrrolyl)-3-methylcycloocta[*b*]pyrrole-2-carboxylate (1.00 g) and palladium/charcoal (10%, 400 mg) by the procedure detailed previously, except the reaction vessel was shaken under hydrogen at 40 psi for 7 days (the reaction failed to go to completion unless prolonged reaction times were used). The desired product was isolated as pink crystals (577 mg; 88%), mp 118.5°C, dec; ^1H NMR ($CDCl_3$): δ 1.2-2.0 (8H, m, 4 x CH_2), 1.82 (3H, s), 2.26 (3H, s), 2.28 (3H, s) (3 x pyrrole-CH_3), 2.50 (1H, m), 2.76 (1H, m) (pyrrole-CH_2), 4.35 (1H, m, bridge-CH), 9.50 (1H, br s), 10.10 (1H, br s) (2 x NH). Anal. calc. for $C_{19}H_{24}N_2O_4.{}^1/_2H_2O$: C, 64.57; H, 7.13; N, 7.92. Found: C, 64.68; H, 7.11; N, 7.44.

9-(5-Carboxy-4-ethyl-3-methyl-2-pyrrolyl)-3-methylcycloocta[*b*]pyrrole-2-carboxylic Acid (**32b**): Prepared from benzyl 9-(5-benzyloxycarbonyl-4-ethyl-3-methyl-2-pyrrolyl)-3-methylcycloocta[*b*]pyrrole-2-carboxylate (500 mg) by the procedure described previously. The title dipyrrole dicarboxylic acid was isolated as a pale pink solid (295 mg; 89%), mp 137°C, dec; ^1H NMR

($CDCl_3$): δ 0.93 (3H, t, CH_2CH_3), 1.2-1.9 (8H, m, 4 x CH_2), 2.29 (6H, s, 2 x pyrrole-CH_3), 2.36 (2H, m, CH_2CH_3), 2.50 (1H, m), 2.78 (1H, m) (pyrrole-CH_2CH_2), 4.38 (1H, m, bridge-CH), 9.7 (1H, br s), 10.2 (1H, br s) (2 x NH). Anal. calc. for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.81. Found: C, 67.05; H, 7.41; N, 8.08.

3,5-Butano-13,17-diethyl-2,7,8,12,18-pentamethylporphyrin (**4a**): A solution of *p*-toluenesulfonic acid monohydrate (150 mg) in methanol (2.5 mL) was added to a stirred solution of 8-(5-carboxy-3,4-dimethyl-2-pyrrolyl)-3-methylcyclohepta[*b*]pyrrole-2-carboxylic acid (100 mg) and 3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrrylmethane-5,5'-dialdehyde (82 mg) in dichloromethane (25 mL) and methanol (2.5 mL). After few minutes, a deep red-orange solution was formed. After stirring at room temperature overnight in the dark (λ_{max} 418, 480 nm), a saturated solution of zinc acetate in methanol (3 mL) was added to the mixture, and the resulting solution was allowed to stir in the dark for a further 2 days at room temperature. The mixture was washed successively with water (50 mL), 5% hydrochloric acid solution (2 x 50 mL), 5% ammonia solution (50 mL) and water (50 mL). The organic layer was evaporated under reduced pressure, and the residue chromatographed on grade III alumina, eluting with dichloromethane. The colored fractions were evaporated under reduced pressure and further purified on a silica column (deactivated by water, 10 mL:100 g), eluting with toluene. The red band was collected and recrystallized from chloroform-methanol to give the title porphyrin (33 mg; 23%) as purple crystals, mp 291°C, dec. UV/Vis (CH_2Cl_2): λ_{max} ($\log_{10}\varepsilon$) 403 (5.29), 504 (4.15), 538 (3.75), 574 (3.77), 627 nm (3.13). ^{1}H NMR ($CDCl_3$): δ -3.24 (2H, br s, 2 x NH), 1.83 (6H, t, 2 x CH_2CH_3), 2.31 (2H, m), 2.73 (2H, m) ($CH_2(CH_2)_2CH_2$), 3.55 (3H, s), 3.56 (3H, s), 3.59 (3H, s), 3.61 (6H, s) (5 x porphyrin-CH_3), 3.81 (2H, m, β-CH_2), 3.96-4.09 (4H, 2 overlapping quartets, 2 x CH_2CH_3), 4.77 (2H, t, *meso*-CH_2), 9.85 (1H, s), 10.00 (1H, s), 10.04 (1H, s) (3 x *meso*-H). FAB MS: m/z 491 ($[M+H]^+$); EI MS: m/z (relative intensity) 490 (100, M^+), 446 (7.5); HR MS calcd. for $C_{33}H_{38}N_4$: 490.30965. Found: 490.30980.

3,5-Butano-7,13,17-triethyl-2,8,12,18-tetramethylporphyrin (**4b**): Prepared from the foregoing procedure from 8-(5-carboxy-4-ethyl-3-methyl-2-pyrrolyl)-3-methylcyclohepta[*b*]-pyrrole-2-carboxylic acid (200 mg) and 3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrrylmethane-5,5'-dialdehyde (158 mg). Recrystallization from chloroform-methanol afforded the butanoporphyrin (73 mg; 26%) as purple crystals, mp 287°C, dec; UV/Vis (CH_2Cl_2): λ_{max} ($\log_{10}\varepsilon$) 404 (5.29), 504 (4.17), 538 (3.76), 574 (3.78), 627 nm (3.16); ^{1}H NMR ($CDCl_3$): δ -3.16 (2H, br s, 2 x NH), 1.85 (9H, 3 overlapping triplets, 3 x CH_2CH_3), 2.35 (2H, m), 2.78 (2H, m) ($CH_2(CH_2)_2CH_2$), 3.58 (6H, s), 3.65 (3H, s), 3.66 (3H, s) (4 x porphyrin-CH_3), 3.86 (2H, m, β-CH_2CH_2), 3.97-4.17 (6H, 3 overlapping quartets, 3 x CH_2CH_3), 4.84 (2H, t, *meso*-CH_2), 9.87 (1H, s), 10.05 (1H, s), 10.07 (1H, s) (3 x *meso*-H); FAB MS: m/z 505 ($[M+H]^+$); EI MS: m/z (relative intensity) 504 (100, M^+), 489 (6); HR MS calcd. for $C_{37}H_{42}N_4$: 504.32396. Found: 504.32459.

3,5-Pentano-13,17-diethyl-2,7,8,12,18-pentamethylporphyrin (**4c**): Prepared from 9-(5-carboxy-3,4-dimethyl-2-pyrrolyl)-3-methylcycloocta[*b*]pyrrole-2-carboxylic acid (200 mg) and 3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrrylmethane-5,5'-dialdehyde (158 mg) as described previously for **4a**. Recrystallization from chloroform-methanol gave the desired porphyrin (34 mg; 12%) as purple crystals, mp 300°C, dec; UV/Vis (CH_2Cl_2): λ_{max} ($\log_{10}\varepsilon$) 403 (5.27), 502 (4.17), 536 (3.74), 571 (3.79), 625 nm (3.17); ^{1}H NMR ($CDCl_3$): δ -3.10 (1H, br s), -2.95 (1H, br s) (2 x NH), 1.49 (2H, m, $(CH_2)_2$-CH_2-$(CH_2)_2$), 1.84 (6H, t, 2 x CH_2CH_3), 2.20 (2H, m), 2.60 (2H, m) ($CH_2CH_2CH_2CH_2CH_2$), 3.60 (3H, s), 3.62 (12H, s) (5 x porphyrin-CH_3), 4.03 (4H, m, 2 x CH_2CH_3), 4.24 (2H, m, β-CH_2CH_2), 5.24 (2H, m, *meso*-CH_2), 9.84 (1H, s), 10.08 (1H, s), 10.13 (1H, s) (3 x *meso*-H); FAB MS: m/z 505 ($[M+H]^+$); EI MS: m/z (relative intensity) 504 (100, M^+), 489 (7.6); HR MS calcd. for $C_{34}H_{40}N_4$: 504.32396. Found: 504.32459.

3,5-Pentano-7,13,17-triethyl-2,8,12,18-tetramethylporphyrin (**4d**): Prepared similarly from 9-(5-carboxy-4-ethyl-3-methyl-2-pyrrolyl)-3-methylcycloocta[*b*]pyrrole-2-carboxylic acid (200 mg) and 3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrrylmethane-5,5'-dialdehyde (152 mg). Recrystallization with chloroform-methanol yielded the title porphyrin (43 mg; 16%) as purple crystals, mp 293°C, dec; UV/Vis (CH_2Cl_2): λ_{max} ($\log_{10}\varepsilon$) 404 (5.28), 504 (4.17), 537 (3.74), 572 (3.78), 627 nm (3.19); ^{1}H NMR ($CDCl_3$): δ -3.05 (1H, br s), -2.85 (1H, br s) (2 x NH), 1.52 (2H, m, $(CH_2)_2$-CH_2-$(CH_2)_2$), 1.53-1.89 (9H, 3 overlapping triplets, 3 x CH_2CH_3), 2.18 (2H, m), 2.62 (2H, m) ($CH_2CH_2CH_2CH_2CH_2$), 3.61 (3H, s), 3.64 (3H, s), 3.65 (3H, s), 3.68 (3H, s) (4 x porphyrin-CH_3), 3.99-4.10 (4H, 3 overlapping quartets, 3 x CH_2CH_3), 4.28 (2H, t, β-CH_2CH_2), 5.28 (2H, m, *meso*-CH_2), 9.85 (1H, s), 10.12 (1H, s), 10.16 (1H, s) (3 x *meso*-H); ^{1}H NMR (TFA-$CDCl_3$): δ -3.46 (2H, br s), -2.71 (1H, br s), -2.49 (1H, br s) (4 x NH), 1.20 (2H, m, $(CH_2)_2$-CH_2-$(CH_2)_2$), 1.63-1.73 (9H, 3 overlapping triplets, 3 x CH_2CH_3), 2.07 (2H, m), 2.57 (2H, m) ($CH_2CH_2CH_2CH_2CH_2$), 3.32 (3H, s), 3.41 (3H, s), 3.50 (6H, s) (4 x porphyrin-CH_3), 3.61 (2H, q), 3.93-4.02 (4H, 2 overlapping quartets) (3 x CH_2CH_3), 4.08 (2H, t, β-CH_2CH_2), 5.25 (2H, m, *meso*-CH_2), 10.13 (1H, s), 10.26 (1H, s), 10.34 (1H, s) (3 x *meso*-H); FAB MS: m/z 519 ($[M+H]^+$); EI MS: m/z (relative intensity) 518 (100, M^+), 446 (5); HR MS calcd. for $C_{35}H_{42}N_4$: 518.34095. Found: 518.34131.

Acknowledgements: This material is based upon work supported by the National Science Foundation under Grant Nos. CHE-9201149 and CHE-9500630, the Donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University Research Fund of Illinois State University. JAB received the following awards in support of these studies: Undergraduate Research Award from Baxter Healthcare Corp. for the Spring semester of 1991; student research grant from the Illinois State Academy of Science, Spring 1992; ACS Organic Division Student Travel Award from Johnson and Johnson to attend the 203rd National Meeting of the American Chemical Society, San Francisco, CA, April 1992.

REFERENCES AND NOTES

1. Part 11: Novak, B.H.; Lash, T.D. *J. Org. Chem.* **1998**, submitted.
2. Results presented, in part, at the 84th Annual Meeting of the Illinois State Academy of Science, University of Illinois at Chicago, Chicago, Illinois, Oct. 1991 (Abstract: Bastian, J.A.; Lash, T.D. *Trans. Ill. St. Acad. Sci.* **1991**, *Suppl. to Vol. 84*, 42); 203rd National Meeting of the American Chemical Society, San Francisco, California, April 1992 (Abstract: Bastian, J.A.; Lash, T.D., *Book of Abstracts*, CHED 98); 85th Annual Meeting of the Illinois State Academy of Science, Springfield, Illinois, Oct. 1992 (Abstract: Bastian, J.A.; Lash, T.D. *Trans. Ill. St. Acad. Sci.* **1992**, *Suppl. to Vol. 85*, 45).
3. Baker, E.W.; Palmer, S.E. In *The Porphyrins*, Ed. Dolphin, D.; **1978**, Vol. 1, pp 486-552; Academic Press, New York. Callot, H.J. In *The Chlorophylls*, Scheer, H., Ed.; CRC Press, Boca Raton, **1991**, pp 339-364.
4. Fischer, H.; Hofmann, H.J. *Justus Liebigs Ann. Chem.* **1935**, *517*, 274; Sugihara, J.M.; McGee, L.R. *J. Org. Chem.* **1957**, *22*, 795; Baker, E.W.; Corwin, A.H.; Klesper, E.; Wei, P.E. *J. Org. Chem.* **1968**, *33*, 3144; Flaugh, M.E.; Rapoport, H. *J. Am. Chem. Soc.* **1968**, *90*, 6877; Chaudry, I.A.; Clezy, P.S.; Mirza, A.H. *Aust. J. Chem.* **1980**, *33*, 1095; Evstigneeva, R.P. *Pure Appl. Chem.* **1981**, *53*, 1129; Pomonarev, G.V.; Shul'ga, A.M.; Subock, V.P. *Dokl. Akad. Nauk SSSR* **1981**, *259*, 1121; Pomonarev, G.V. *Khim. Geterotsikl. Soedin.* **1981**, 1693; Smith, K.M.; Langry, K.C.; Minnetian, O.M. *J. Org. Chem.* **1984**, *49*, 4602; Bauder, C.; Ocampo, R.; Callot, H.J. *Synlett* **1990**, 335; *ibid.*, *Tetrahedron Lett.* **1991**, *32*, 2537; Clezy, P.S.; Mirza, A.H.; Prashar, J.K. *Aust. J. Chem.* **1990**, *43*, 857; Clezy, P.S.; Van Phuc, L.; Prashar, J.K. *ibid.* **1991**, *44*, 1061.
5. Clezy, P.S.; Prashar, J.K. *Aust. J. Chem.* **1990**, *43*, 825; Clezy, P.S.; Jenie, U.; Prashar, J.K. *ibid.*, 839.
6. Lash, T.D. *Org. Geochem.* **1989**, *14*, 213. 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. Lash, T.D.; Quizon-Colquitt, D.M.; Shiner, C.M.; Nguyen, T.H.; Hu, Z. *Energy Fuels*, **1993**, *4*, 668. Lash, T.D. In *Advances in Nitrogen Heterocycles*; Moody, C.J., Ed.; JAI Press, **1995**, Vol. 1, 19-51.
7. Lash, T.D.; Balasubramaniam, R.P. *Tetrahedron Lett.* **1990**, *31*, 7545. Lash, T.D.; Bladel, K.A.; Shiner, C.M.; Zajeski, D.L.; Balasubramaniam, R.P. *J. Org. Chem.* **1992**, *57*, 4809. May, D.A., Jr.; Lash, T.D. *J. Org. Chem.* **1992**, *57*, 4820. Lash, T.D.; Nguyen, T.H.; Hu, Z. *Synlett* **1994**, 905. Hu, Z.; Lash, T.D. *Synlett* **1994**, 909. Chen, S.; Lash, T.D. *J. Heterocyclic Chem.* **1997**, *34*, 273.
8. a. Lash, T.D.; Johnson, M.C. *Tetrahedron Lett.* **1989**, *30*, 5697. b. Lash, T.D.; Perun, T.J., Jr. *ibid.* **1987**, *28*, 6265.
9. Lash, T.D.; Catarello, J.J. *Tetrahedron* **1993**, *49*, 4159. Quizon-Colquitt, D.M.; Lash, T.D. *J. Heterocyclic Chem.* **1993**, *30*, 477.
10. a. Lash, T.D. *Tetrahedron Lett.* **1988**, *29*, 6877; b. Lash, T.D. *Tetrahedron* **1998**, *54*, 359.
11. E.g.: Urbach, H.; Henning, R. *Tetrahedron Lett.* **1985**, *26*, 1839. Caspritz, G.; Alpermann, H.G.; Schleyerbach, R. *Arzeim.-Forsch.* **1986**, *36*, 1605.
12. Jackson, A.H.; Smith, K.M. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed., **1973**, Vol. 1, pp 143-234, Wiley, New York. Ibid., **1984**, Vol. 6, pp 237-280.
13. a. Smith, K.M.; Kehres, L.A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2329. b. Smith, K.M.; Minnetian, O.M. *J. Org. Chem.* **1985**, *50*, 2073.
14. Terry, W.G.; Jackson, A.H.; Kenner, G.W.; Kornis, G. *J. Chem. Soc.* **1965**, 4389.
15. Lash, T.D.; Hoehner, M.C. *J. Heterocyclic Chem.* **1991**, *28*, 1671.
16. Cook, K.L.; Waring, A.J. *J. Chem. Soc., Perkin Tans. 1* **1973**, 529.
17. Surber, W.; Schinz, H. *Helv. Chim. Acta* **1954**, *37*, 1239.
18. Prepared by adapting the procedure for ethyl 3-butylacetoacetate: Marvel, C.S.; Hager, F.D. *Org. Synth.* **1932**, Coll. Vol. I, pp 248-250.
19. Lash, T.D.; Bellettini, J.R.; Bastian, J.A.; Couch, K.B. *Synthesis*, **1994**, 170. See also: Burns, D.H.; Jabara, C.S.; Burden, M.W. *Synth. Comm.* **1995**, *25*, 379. This strategy involves the condensation of nitroalkenes, or the related α-acetoxy-nitroalkanes with benzyl isocyanoacetate in the presence of a non-nucleophilic base and is based on ealier studies by others. See: Barton, D.H.R.; Kervagoret, J.; Zard, S.Z. *Tetrahedron* **1990**, *46*, 7587.
20. Arsenault, G.P.; Bullock, E.; MacDonald, S.F. *J. Am. Chem. Soc.* **1960**, *82*, 4384. Cavaleiro, J.A.S.; Rocha Gonsalves, A.M. d'A.; Kenner, G.W.; Smith, K.M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1771.
21. Rankin, J.G.; Czernuszewicz, R.S.; Lash, T.D. *Org. Geochem.*, **1995**, *23*, 419. Rankin, J.G.; Czernuszewicz, R.S.; Lash, T.D. *Inorg. Chem.*, **1995**, *34*, 3025. Czernuszewicz, R.S.; Rankin, J.G.; Lash, T.D. *Inorg. Chem.*, **1996**, *35*, 199.