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Synthesis of Deoxophylloerythroetioporphyrin (DPEP) and Three Ring Homologs by an Improved *b*-Bilene Methodology

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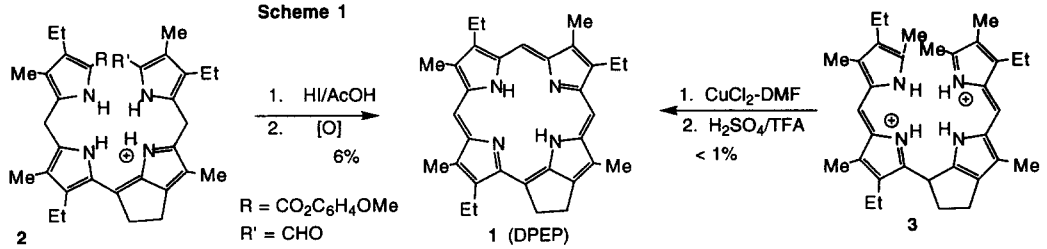
Abstract: *Deoxophylloerythroetioporphyrin, an important porphyrin molecular fossil from oil shales and petroleum, and three homologs with six-, seven- or eight-membered exocyclic rings have been prepared by a one pot cyclization of b-bilenes with TFA-trimethyl orthoformate in dichloromethane.* © 1998 Elsevier Science Ltd. All rights reserved.

Deoxophylloerythroetioporphyrin (DPEP; **1**) is a common molecular fossil found in oil shales, petroleum and other organic-rich sediments.[1] The five-membered exocyclic ring of DPEP derives from chlorophyll and for this reason many other naturally occurring petroporphyrins also bear this structural unit. DPEP has been targeted for synthesis by many research groups over the years,[2-6] but all of these methodologies are flawed in one way or another and afford relatively poor overall yields. Attempts to cyclize tetrapyrrolic intermediates incorporating the five-membered carbocyclic ring have previously given very poor yields of desired porphyrin products.[4,6] Cyclization of *b*-bilene **2** with HI-acetic acid was claimed to give **1** in 6% yield,[4] while copper(II) chloride mediated cyclization of *a,c*-biladiene **3** afforded no more than trace amounts of porphyrin[6] (Scheme 1). On the other hand, MacDonald condensation[7] of dipyrrylmethanes **4** with dialdehydes **5** under conventional conditions gave relatively good yields (18-20%) of the type II *meso*,β-ethanoporphyrins **6** (Scheme 2).[6] These differences were rationalised in terms of the hybridization levels for the linking carbon atom within the cyclopentene subunit. In **2**, the conjugated pyrromethene portion of the tetrapyrrole holds the five-membered ring in close proximity to the adjacent ethyl moiety and this deleterious interaction disfavors macrocyclic ring formation. In **3**, the sp^3 hybridized bridging carbon atom orientates the ring away from the ethyl group but this species must undergo conversion to a fully conjugate bilatriene prior to cyclization and this introduces the same steric problems.[6,8,9] On the other hand, the "2 + 2" MacDonald cyclization occurs while the critical bridging carbon remains sp^3 hybridized and this relieves steric interactions during the formation of the porphodimethene intermediate **7**.[6,8] Subsequent air oxidation in the presence of zinc acetate then gives the *meso*,β-ethanoporphyrin **6**, albeit with the non-natural type II arrangement of substituents.

Scheme 1



2 **1** (DPEP) **3**

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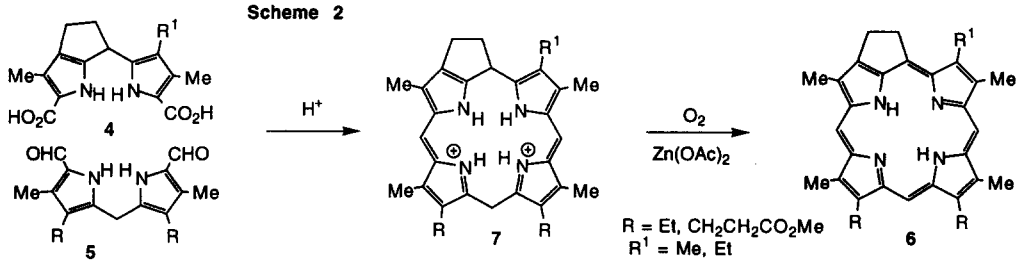
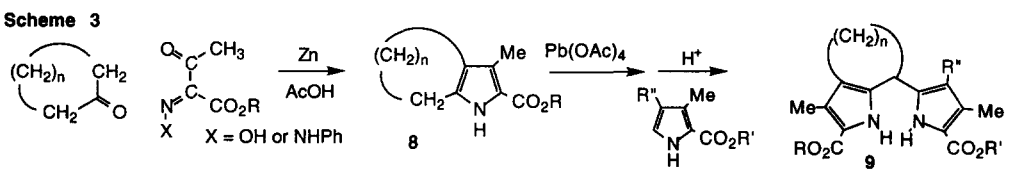
Scheme 2



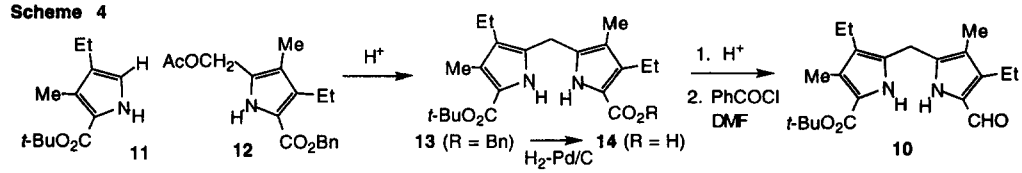
Alternative routes to DPEP and related structures have been developed where the carbocycle is introduced subsequent to porphyrin formation,[5] but the increased number of steps takes a heavy toll on the overall yields for these syntheses. The availability of synthetic cycloalkanoporphyrins has been an essential to the development of new analytical methods for petroporphyrin analysis,[10,11] but the difficulty in obtaining the natural *meso*,β-ethanoporphyrins has limited these investigations. The MacDonald route cannot be used to synthesize DPEP because one of the two condensing dipyrroles must be symmetrical to avoid isomer formation. However, stepwise versions of the MacDonald condensation have been reported utilizing *b*-bilene intermediates,[4,12] and we set out to adapt this approach for the synthesis of cycloalkanoporphyrins.

During the course of our earlier studies, we developed superior routes to cyclopenta[*b*]pyrroles[13] and related ring homologs **8**,[8,13,14] and their conversion via a 2 step procedure to give structurally diverse dipyrroles **9** (Scheme 3). These provided the key building blocks for the current study. A dipyrrylmethane monoaldehyde **10** was required for the upper portion of DPEP and this was prepared in three steps from pyrroles **11** and **12** (Scheme 4). Condensation of **11** and **12** in the presence of Montmorillonite clay[15] gave excellent yields of the mixed ester dipyrrylmethane **13** and subsequent hydrogenolysis over 10% Pd/C afforded the related carboxylic acid **14**. Decarboxylation with 2 equiv. of *p*-toluenesulfonic acid, followed by formylation with benzoyl chloride-DMF gave the required aldehyde **10**.

Scheme 3

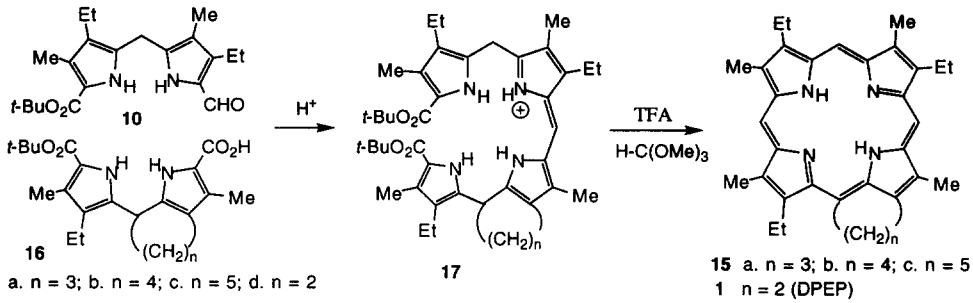


Scheme 4



In relation to our ongoing investigations on the applications of vibrational spectroscopy to the analysis of petroporphyrins,[11] a series of porphyrins **15a-c** with varying ring sizes were required in addition to DPEP. The chemistry of porphyrins with fused six-membered rings[8,16] had received the greatest attention in our previous investigations and for this reason the *meso*,β-propanoporphyrin **15a** was initially targeted for synthesis. A series of dipyrrole carboxylic acids **16a-c** incorporating carbocyclic rings and *tert*-butyl ester protective groups on the opposite terminus were prepared by hydrogenolysis of the corresponding benzyl esters (Scheme 5). Treatment of **16a** with aldehyde **10** with 2 equiv. of *p*-toluenesulfonic acid in dichloromethane afforded the corresponding *b*-

Scheme 5



bilene **17a**.[17] This was converted to the hydrochloride salt by brief treatment with dry HCl but attempts to crystallize this species were unsuccessful. Instead the crude tetrapyrrole was deprotected with TFA and cyclized under literature conditions with trimethyl orthoformate and trichloroacetic acid. While this procedure apparently works quite well in the synthesis of β-octasubstituted porphyrins, in our hands very poor yields of impure porphyrin **15a** were obtained by this approach. The procedure requires the extraction of the relatively unstable deprotected *b*-bilene, followed by drying over magnesium sulfate and solvent evaporation. Inspired by our recent successes in utilizing tripyrranes with terminal *tert*-butyl ester protective units in a one pot deprotection-"3 + 1" synthesis of porphyrins,[18] we speculated that a similar procedure could give superior results for *b*-bilene cyclizations. TFA is initially required to cleave the *tert*-butyl ester units, but this might also function as the acid catalyst for the cyclization. Hence, following a 10 min. pretreatment of **17a** with TFA, the reaction mixture was diluted with CH_2Cl_2 and a slight excess of $CH(OMe)_3$ was added via a syringe.[17] The mixture was stirred at room temperature under nitrogen for 2 h, neutralized with Et_3N and oxidized with DDQ. Following chromatography on Grade 3 neutral alumina and recrystallization from chloroform-methanol, the DPEP ring homolog **15a** was isolated in 31-38% yield. These conditions were also applied to the synthesis of the related seven- and eight-membered ring structures from **16b** and **16c**, respectively. The *meso*,β-butanoporphyrin **15b** was obtained 30-32% yield, while the eight-membered ring porphyrin **15c** was obtained in an impressive 50-51% yield. This latter result is somewhat surprising because the eight-membered ring system gave relatively poor results in the MacDonald condensation (Scheme 2). Although further studies will be required to fully explain these results, this version of the *b*-bilene methodology clearly provides an excellent direct route to type III cycloalkanoporphyrins.

Unfortunately, the five-membered ring system gave poor results in these studies. We speculated that this was due to the instability of *b*-bilene **17d** which appeared to decompose during work-up. Similar problems had been encountered for the "2 + 2" condensation when attempts were made to isolate deprotected dipyrroles incorporating a five-membered carbocyclic ring, and this was attributed to decreased stability of the intermediates due to ring strain.[6,8] In order to combat these problems, the *b*-bilene was generated in the presence of 1 equiv. of *p*-toluenesulfonic acid (2 h), the solvent evaporated and deprotection-cyclization immediately carried out on the crude material. Following air oxidation in the presence of zinc acetate, the resulting product was converted to the nickel(II) complex[19] and purified by flash chromatography to remove contamination by etioporphyrin which is formed by self-condensation of **10**. Following recrystallization from chloroform-methanol, DPEP was obtain in 14-22% yield. Although the results are more modest in this case, they still represent the best yields reported so far for DPEP starting from dipyrrolic intermediates.

In conclusion, a modified one pot methodology for the deprotection and cyclization of *b*-bilenes has been shown to give excellent yields of cycloalkanoporphyrins with 6-8 membered exocyclic rings. While the results are less successful for DPEP itself, they are superior to any known route to this system. This approach will also allow the synthesis of many related geoporphyrins to be accomplished.

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17. Sample Procedure: Propanoporphyrin **15a**: In a 100 mL round bottomed flask, **16a** (300 mg) and **10** (278 mg) were dissolved in CH_2Cl_2 (45 mL). A solution of *p*-toluenesulfonic acid (591 mg) in MeOH (7.2 mL) was added, and the resulting mixture stirred under nitrogen at room temperature for 30 min. The dark red solution was washed with 5% sodium carbonate solution and water and dried over sodium sulfate. Evaporation of the solvent under reduced pressure afforded the tetrapyrrolic intermediate **17a** (*b*-bilene). The dark residue was then dissolved in CH_2Cl_2 (10 mL) and hydrogen chloride gas was bubbled through the solution for 5 sec to form the hydrochloride salt. Immediately, the solvent was evaporated and the residue taken up twice in toluene and evaporated in order to remove traces of water and HCl. The resulting crude *b*-bilene (quantitative) could not be recrystallized and was generally used immediately. TFA (1 mL) was added to the *b*-bilene (100 mg) and the mixture was stirred under nitrogen for 10 min. The mixture was diluted with CH_2Cl_2 (20 mL) and then trimethyl orthoformate (0.0325 ml) was added to the stirred solution. The mixture was stirred in the dark and under nitrogen for 2 h. Triethylamine was added dropwise to neutralize the TFA, DDQ (31.6 mg) was added immediately and the resulting solution stirred in the dark and under nitrogen for another additional 1 h. The solution was washed with water, the solvent removed under reduced pressure and the residue chromatographed on a grade 3 alumina column, eluting with CH_2Cl_2. Evaporation of the solvent and recrystallization from chloroform-methanol afforded the porphyrin as violet-red crystals (21 mg; 31%), mp 284-286°C; ^{1}H NMR ($CDCl_3$): -3.30 (1H, br s), -3.32 (1H, br s) (2 x NH), 1.80 (3H, t), 1.87 (6H, t) (3 x CH_2CH_3), 2.88 (2H, m, $CH_2CH_2CH_2$), 3.59 (3H, s), 3.63 (3H, s), 3.66 (3H, s), 3.84 (3H, s) (4 x porphyrin-CH_3), 3.86 (2H, t, 13^1-CH_2), 4.01 (2H, q), 4.12 (4H, q) (3 x CH_2CH_3), 5.12 (2H, t, 13^3-CH_2), 9.89 (1H, s), 10.03 (1H, s), 10.09 (1H, s) (3 x *meso*-H). HR MS: Calc. for $C_{33}H_{38}N_4$: 490.30960. Found: 490.30965.
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19. The free base of DPEP readily oxidizes on silica gel during chromatography but this complication can be minimized by converting the porphyrin to its nickel(II) complex which is reasonably stable under these conditions. See: Krane, J.; Skjetne, T.; Telnaes, N.; Bjoroy, M.; Schou, L.; Solli, H. *Org. Geochem.* **1984**, *6*, 193. Clezy, P.S.; Mirza, A.H.; Prashar, J.K. *Aust. J. Chem.* **1990**, *43*, 857. Hu, Z.; Lash, T.D. *Synlett* **1994**, 909.