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TOTAL SYNTHESES OF N-METHYLPROTOPORPHYRINS-IX

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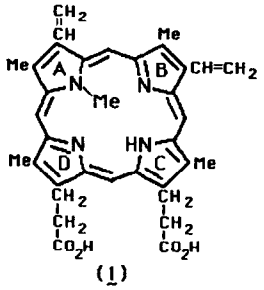
Abstract: Routes for the total syntheses of the N-methylprotoporphyrin-IX dimethyl esters (2)-(5) are described.

N-Methylprotoporphyrin-IX (1) has been shown[1-3] to be a suicide inhibitor of the enzyme ferrochelatase. As a mixture of the four isomeric N-methylated pigments, the compound has been used[4] for study of the biosynthetic pathways to hemes, chlorophylls and phycobilins. In was also shown[5] that the N-methylprotoporphyrin-IX of major pharmacological significance has the N-methyl group located on the ring A nitrogen atom, i.e. compound (1). Since that time, and though all N-methylprotoporphyrin-IX isomers appear to inhibit ferrochelatase activity, there has been a clear need for moderately large quantities of pure N-methylprotoporphyrin-IX isomers, and this need cannot be filled by the tedious separation[5] of the four N-methyl protoporphyrin-IX isomers prepared using methyl iodide or methyl fluorosulfonate.[6]



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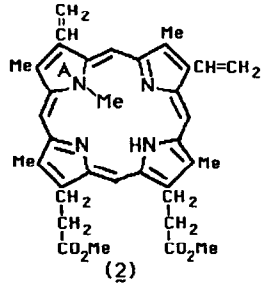

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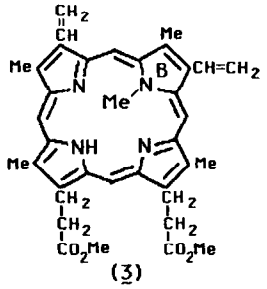

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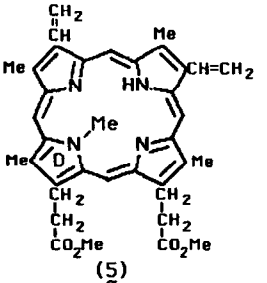

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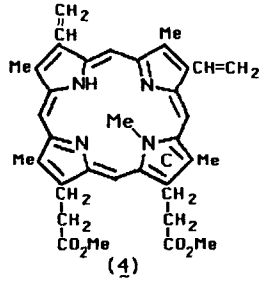

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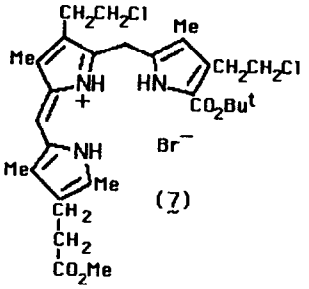

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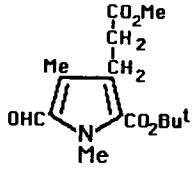

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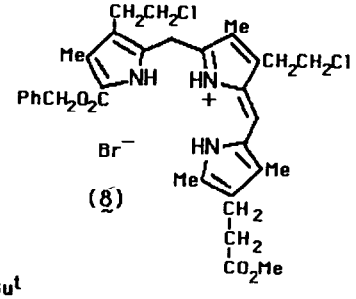

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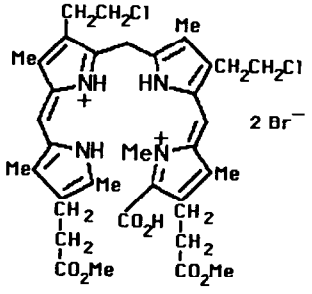

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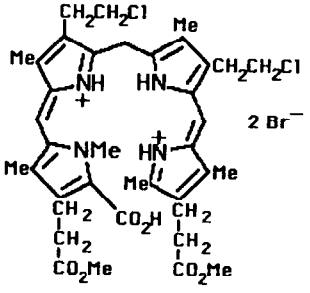

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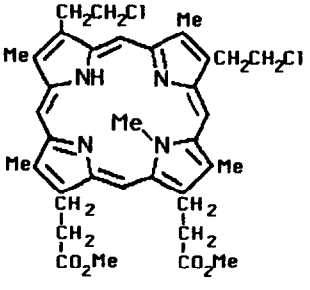

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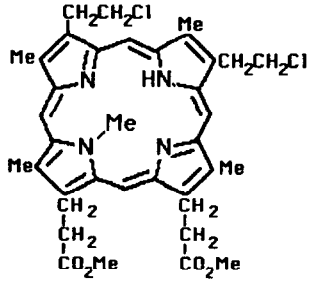

(12)

Jackson et al.[7] recently showed that N-methyl groups are not cleaved in the MacDonald pyrromethane approach,[8] and thereby successfully prepared a model N-methylporphyrin by total synthesis. In work to be described elsewhere,[9] we have successfully used this type of approach to synthesize all four N-methylprotoporphyrin-IX dimethyl esters (2)-(5). Compounds (2) and (3) were obtained without significant problems,[10] but, as a consequence of the symmetry restrictions inherent in the MacDonald approach,[11] the N-methylprotoporphyrin-IX isomers, (4) and (5) were only obtained as a mixture which must be subsequently separated using arduous high performance liquid chromatography.[5]

Use of the general route involving copper(II) catalyzed cyclization of 1',8'-dimethyl-a,c-biladienes in boiling dimethylformamide[12] or at room temperature[13] resulted in production of porphyrin in the cyclization step from which the N-methyl group had been cleaved. However, we have discovered that cyclization of N-methyl-a,c-biladienes (e.g. 9, 10) with iodine and bromine in o-dichlorobenzene[14] affords the required N-methylporphyrin in good yield. In this way, the symmetry limitations of the MacDonald approach were circumvented.

Thus, the a,c-biladienes (9)[15] and (10) were prepared from the corresponding tripyrrenes (7) and (8)[16] by condensation with the N-methylformylpyrrole (6).[17] Treatment of the resulting a,c-biladienes (9) and (10) with five equivalents of iodine and two equivalents of bromine in refluxing o-dichlorobenzene for 20 min gave the porphyrins (11) and (12) in 20 and 22% yield, respectively. Dehydrohalogenation with KOH/pyridine gave the required N-methylprotoporphyrins (4; 45%) and (5, 50%).[18] These compounds[19] had spectroscopic properties identical with those described by Ortiz de Montellano and Kunze.[5] Figure 1 shows the characteristic low field and high field regions in the proton NMR spectra of compounds (4) and (5).

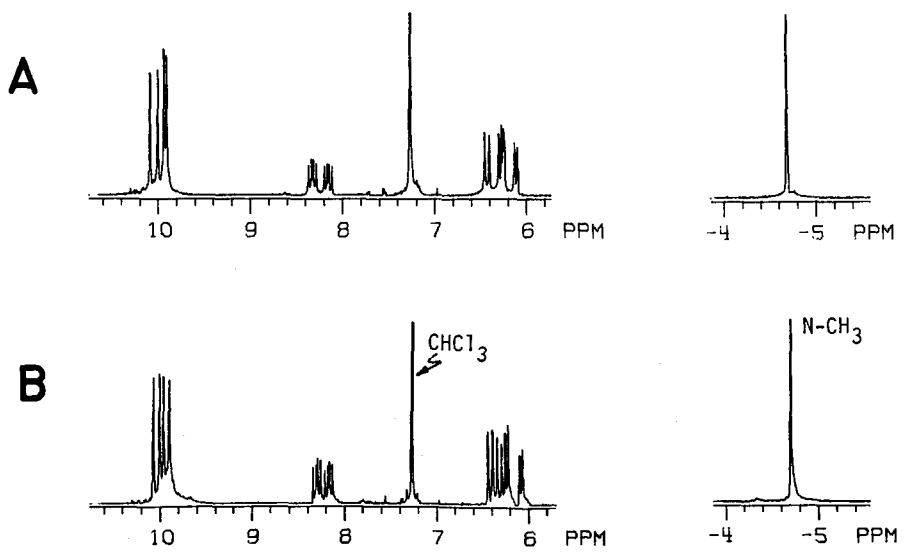

Figure 1: High and low field regions in the 360 MHz proton NMR spectra (in $CDCl_3$) of (A) N_C-methylprotoporphyrin-IX dimethyl ester (4), and (B) N_D-methylprotoporphyrin-IX dimethyl ester (5).

Acknowledgement

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10. M.p. compound (2), 148-153°C; m.p. compound (3), 148-151°C.
11. For a discussion, see K. M. Smith, in "Porphyrins and Metalloporphyrins", K. M. Smith, ed., Elsevier, Amsterdam, 1975, pp. 33-36, 47-48.
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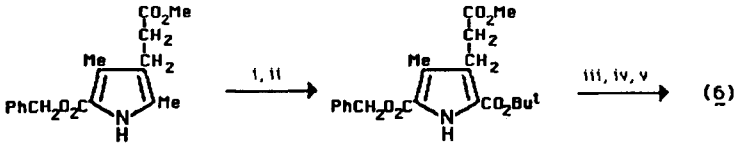
14. V.D. Rumyantseva, A.F. Mironov, R.P. Evstigneeva, A.N. Stepanov, A.A. Perov and S.E. Kupriyanov, Z. Org. Khim., 1979, 49, 883.
15. All new compounds gave satisfactory NMR spectra, elemental analyses, and/or high resolution mass spectra.
16. Tripyrrenes were obtained by way of standard methodology; see Ref. 12.
17. Pyrrole (6) was synthesized as follows:



Reagents: i, SO_2Cl_2 ; ii, $Bu^tOH/NaOAc$; iii, MeI/KOH; iv, H_2/Pd-C; v, $POCl_3$/DMF

18. Yields in this step have not been optimized.
19. M.p. compound (4), 75-77°C; m.p. compound (5), 101-103°C.

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