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A CONVENIENT SYNTHETIC ROUTE TO THE BACTERIOCHLORIN CHROMOPHORE

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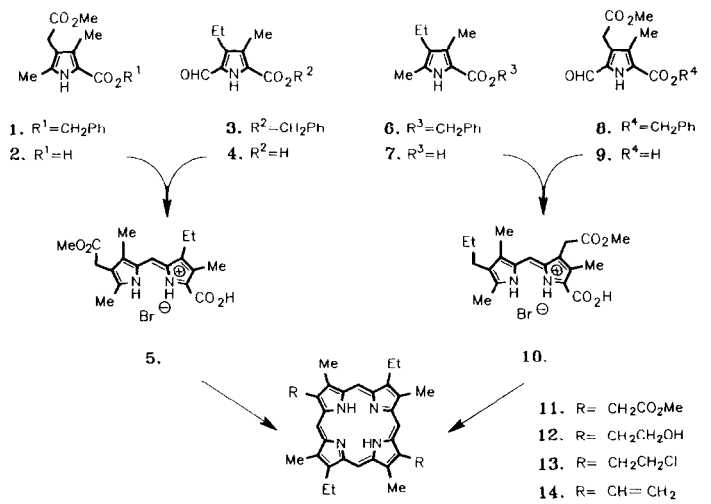
Abstract: The reactions of an A,C-divinylporphyrin with activated dienophiles yield stable bis Diels-Alder adducts absorbing light at wavelengths above 735 nm. This provides a convenient general route to bacteriochlorin-like chromophores.

Photodynamic therapy (PDT)[1] is a novel technique for treating malignant tumors whereby a preferentially localized photosensitizer is activated using light of appropriate wavelength leading to singlet oxygen mediated destruction of the tissue. The sensitizers that have been studied extensively are hematoporphyrin derivative (HpD)[2] and an enriched fraction[3] of it, commercially referred to as Photofrin^R. Photofrin^R is a complex mixture of porphyrin dimers and oligomers having a weak absorption maximum around 630 nm, at which wavelength the tissue penetration of activating light is low. The search for a second-generation photosensitizer which absorbs strongly at a longer wavelength, (thereby conferring a therapeutic advantage of greater tissue penetration) has resulted in the development of several new compounds[4,5] having absorption maxima in the 650-750 nm range. Of particular importance is a "chlorin-type" compound benzoporphyrin derivative (BPD) synthesized in our laboratory by the Diels-Alder reaction of dimethyl acetylenedicarboxylate on protoporphyrin IX dimethyl ester.[6] BPD, with a strong absorption peak at 690 nm has been shown in animal studies[7] to be more useful in PDT than Photofrin^R. With the advent of low-cost reliable diode lasers operating in the 790-850 nm range, the emphasis has been for the development of compounds absorbing in the far visible red and near infra red region. Continuing our work on Diels-Alder reactions of vinylporphyrins, we have developed and describe here, the synthesis of a stable bacteriochlorin system.

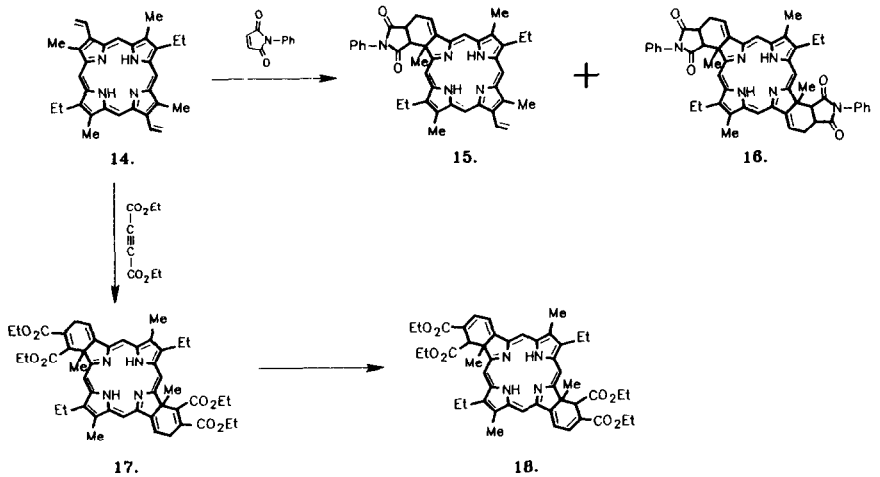
The synthetic strategy adopted here was based on the assumption that two successive Diels-Alder cycloadditions will occur on an A,C-divinylporphyrin. Although vinylporphyrins have been synthesized in high yield[8] employing a stepwise approach via 1-bromo-19-methylbiladienes-ac,[9] we chose to simplify the synthetic route by introducing a two-fold axis of symmetry perpendicular to the porphyrin plane. This allowed the use of a convenient one-pot synthesis[10] for the construction of the porphyrin macrocycle.

Scheme 1 outlines two synthetic approaches to the A,C-divinylporphyrin **14**, using the readily available pyrroles, benzyl 4-methoxycarbonylmethyl-3,5-dimethylpyrrole-2-carboxylate (**1**)[11] and benzyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (**6**).[12] In the first approach, pyrrole **6** was initially transformed to the synthetically useful benzyl 4-ethyl-5-formyl-3-methylpyrrole-2-carboxylate (**3**) using 2 equivalents of sulfuryl chloride in dichloromethane followed by hydrolysis.[13] The pyrroles **1** and **3** were catalytically debenzylated and the resulting carboxylic acids (**2** and **4**) dissolved in refluxing acetonitrile-methanol (1:1) and treated with HBr in acetic acid. The orange-brown solution was evaporated *in vacuo*, and the crude dipyrromethene **5** self-condensed in refluxing anhydrous formic acid using 2.2 equivalents of bromine. Careful evaporation of the solvent followed by the usual work-up afforded the bis(methoxycarbonymethyl)porphyrin **11** in 25-30% overall yield (from **1** and **3**). An alternative route starting from the monopyrroles **6** and **8** (the latter obtained from **1**) via the dipyrromethene **10**, produced the porphyrin **11** in similar overall yield. This was transformed to the A,C-divinylporphyrin **14** in high yield via the bis(2-hydroxyethyl)porphyrin **12** and bis(2-chloroethyl)porphyrin **13** as previously reported.[8]



Scheme 1.

The Diels-Alder reactions of the divinylporphyrin **14** were carried out in degassed toluene solutions at 110°C using a 50 fold molar excess of the appropriate dienophile. The formation of the monoadduct (chlorin) and the bis adduct (bacteriochlorin) could be followed by uv-visible spectroscopy due to characteristic absorption maxima associated with each chromophore. The optimum reaction time was found to be 72 h, beyond which, the transformation of the chlorin to the bacteriochlorin was accompanied by significant decomposition of the product. Reaction of **14** with the olefinic dienophile N-phenylmaleimide under the conditions specified above, gave the bis adducts **16**[14] (Scheme 2) as the major product in 45% yield while the monoadduct **15** was isolated in <8% yield. The electronic spectrum of **16** exhibited a double Soret (λ_{max} = 388, 410 nm) and a strong absorption at 738 nm, a characteristic of the bacteriochlorin chromophore. Reaction of the divinylporphyrin **14** with the acetylenic dienophile, diethyl acetylenedicarboxylate, gave the bis



Scheme 2.

adduct **17**[15] in 52% yield also exhibiting a double Soret and a strong absorption at 738 nm. Treatment of **17** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 3 h at room temperature resulted in a bathochromic shift of the long wavelength absorption up to 786 nm. The ^{1}H nmr spectrum of the product **18**[16] isolated in near quantitative yield, confirmed that the double bond in each six-membered ring had isomerized, thus extending the conjugation in the molecule. Complete structural and stereochemical features were established using n.O.e. difference experiments.

The method described above provide convenient access to stable bacteriochlorin derivatives which have previously been observed[17] as unstable non-isolable reaction products.

Acknowledgements

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14. Analytical data for **16**: mp 185-186°C Vis (CH_2Cl_2): λ_{max} (log ε) 388 (4.99), 410 (5.07), 490 (4.19), 526 (4.05), 702 (3.96), and 738 (4.85) nm; High resolution mass: M^+, 820.3729, $C_{52}H_{46}N_6O_4$ requires 820.3724); ^{1}H-NMR ($CDCl_3$) δ -2.28 (s, 2H, 2 x NH), 1.70 (t, 6H, 2 x $-CH_2\underline{CH_3}$), 2.00, 2.05 (2s, 6H, angular-CH_3), 3.35 (s, 6H, ring-CH_3), 3.40 (m, 4H, $-CH_2-$ at C-2^3 and C-12^3); 3.80 (m, 2H, H at C-2^2 and C-12^2); 3.85 (m, 4H, 2 x $\underline{CH_2}CH_3$); 4.54 (d, 2H, H at C-2^1 and C-12^1); 6.60-7.00 (m, 10H, Ar-H); 7.22 (t, 2H, H at C-2^4 and C-12^4); 8.90, 9.05 (2s, 4H, meso-H).

15. Analytical data for **17**: mp 175-177°C Vis (CH_2Cl_2): λ_{max} (log ε) 384 (5.00), 406 (5.08), 484 (4.21), 538 (4.06), 698 (3.94), and 738 (4.86) nm; High resolution mass: M^+, 814.3957, $C_{48}H_{54}N_4O_8$ requires 814.3927; ^{1}H-NMR ($CDCl_3$) δ -2.51 (s, 2H, 2 x NH), 1.08 (t, 6H, $-CO_2CH_2\underline{CH_3}$ at C-2^1 and C-12^1); 1.40 (t, 6H, $-CO_2CH_2\underline{CH_3}$ at C-2^2 and C-12^2); 2.00, 2.02 (2s, 6H, angular-CH_3 at C-2^1 and C-12^1); 3.40 (s, 6H, 2 x ring-CH_3); 3.62 (m, 2H, H at C-2^3 and C-12^3); 3.85 (m, 4H, 2 x $\underline{CH_2}CH_3$), 3.95 (m, 2H, H at C-2^3 and C-12^3); 4.30-4.40 (m, 4H, 2 x $-CO_2\underline{CH_2}CH_3-$ at C-2^2 and C-12^2); 4.42-4.62 (m, 4H, 2 x $-CO_2\underline{CH_2}CH_3$ at C-2^1 and C-12^1); 7.23-7.28 (m, 2H, H at C-2^4 and C-12^4); 8.95 (s, 2H, H at C-5 and C-15); 9.18 (s, 2H, H at C-10 and C-20).

16. Analytical data for **18**: mp 279-280°C. Vis (CH_2Cl_2): λ_{max} (log ε) 448 (4.89), 468 (5.05), 558 (4.43), 622 (4.58), 702 (4.26), 742 (4.22), and 786 (4.86) nm; High resolution mass: M^+, 814.3957, $C_{48}H_{54}N_4O_8$ requires 814.3927; ^{1}H-NMR ($CDCl_3$) δ -1.87 (br s, 2H, 2 x NH), 0.33, 0.38 (t, 6H, $-CO_2CH_2\underline{CH_3}$ at C-2^1 and C-12^1); 1.46 (t, 6H, $-CO_2CH_2\underline{CH_3}$ at C-2^2 and C-12^2); 1.74, 1.78 (s, 6H, angular-CH_3 at C-2^1 and C-12^1); 1.75 (t, 6H, 2 x $-CH_2\underline{CH_3}$); 3.30-3.60 (m, 4H, $-CO_2\underline{CH_2}CH_3$ at C-2^1 and C-12^1); 3.35 (s, 6H, 2 x ring-CH_3); 3.75-3.90 (m, 4H, 2 x $\underline{CH_2}CH_3$); 4.35-4.50 (m, 4H, $-CO_2\underline{CH_2}CH_3$ at C-2^2 and C-12^2); 4.90 (s, 2H, H at C-2^1 and C-12^1); 7.28, 7.78 (2d, 4H, J = 8 Hz, H at C-2^3, C-2^4, C-12^3 and C-12^4); 8.76 (s, 2H, H at C-5 and C-15); 9.13 (s, 2H, H at C-10 and C-20).

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