Synthesis of Novel Benzobacteriopurpurins by Diels-Alder Cycloaddition

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A new class of stable bacteriochlorins, namely benzobacteriopurpurin bearing two exo-cyclic rings was synthesized by way of Diels-Alder cycloaddition of 8-vinyl-mesopurpurin-18 methyl ester with tetracyanoethylene (TCNE) and dimethyl acetylenedicarboxylate (DMAD). These novel bacteriochlorins have long wavelength absorptions in the range of 760 to 795 nm.

Among tetrapyrrolic systems, chlorins and bacteriochlorins have generated great interest as models for photosynthetic reaction centers in plants and bacteria.[1, 2] Due to their long wavelength absorptions, these classes of compounds have also shown interests as photosensitizers for the treatments of cancers by photodynamic therapy (PDT).[3] Most of the naturally occurring bacteriochlorins[4] tested so far for *in vivo* sensitizing activity are quite unstable with regards to dehydrogenation, and thus the development of methods that efficiently construct stable bacteriochlorins has been a primary target in our group, and in others, over the past several years.

As part of program aimed at developing new methodology and achieving various syntheses of bacteriochlorin systems we initially extended the approach of Chang and co-workers[5] by subjecting various type of chlorins to osmium tetroxide hydroxylation to produce *vic*-dihydroxybacteriochlorin. In our attempts to investigate the stability of certain *vic*-dihydroxybacteriochlorins at high temperature, we often observed the formation of vinyl chlorins. This type of transformatiom had previously been reported by Chang and coworkers[6] in their preparation of vinyl porphyrin from dihydroxy octaethylchlorin by refluxing in benzene containing *p*-toluenesulfonic acid. For quite some time we were interested in introducing vinyl group in ring B (diagonal to reduced pyrrole subunit), so that Diels-Alder cycloaddition reaction could lead to new class of bacteriochlorins. Diels-Alder reaction has been studied in depth by various investigators for a facile conversion of vinyl porphyrins to chlorins.[7-9] A few years ago, we used this methodology for preparing bacteriochlorins by 'double' Diels-Alder reaction of 8,18-divinylporphyrin with various dienophiles.[10] Depending on the nature of dienophiles, these bacteriochlorins had long wavelength absorptions at 720 nm (with TCNE) and 782 nm (with DMAD). However, due to their multistep syntheses, the overall yield of the final products were low. Thus, our main objective was to develop a short synthesis of bacteriochlorins from easily available starting materials.

In order to use Diels-Alder approach to synthesize bacteriochlorins from natural chlorins, methyl pheophorbide-a **1**[11] was converted to mesopurpurin-18 methyl ester **2** and was used[12] as a substrate for our studies. Treatment of **2** with osmium tetroxide, followed by cleavage of the osmate ester with H_2S, afforded the corresponding *vic*-dihydroxypurpurin-18 methyl ester **3** as diasteriomeric mixture in a ratio of 1:1 (*cis*-hydroxy groups up and down relative to ring D) in 80% yield. On refluxing with benzene containing *p*-toluenesulfonic acid[6] diol **3** afforded 8-vinyl- analog **4** in low yield, and mainly the decomposition products were obtained. Several attempts were made to improve the yield of the desired vinyl-chlorin **4** by using various reaction conditions. Interestingly, heating the diol **3** alone in 1, 2-dichlorobenzene at 160 °C for 1h gave 8-vinyl-purpurin-18 methyl ester **4** (λ max 684 nm) in 65% yield. The other product from this reaction was identified as 8-oxobacteriopurpurin **5** (λ max: 711 nm, yield: 20%), in which the ethyl group preferentially migrated over the methyl substituent. The structure of **5** was confirmed by NMR, HRMS and NOE studies. To our knowledge, in tetrapyrrolic systems, this is the first example in which such preferential migration is reported without using any acid catalyst.

The 8-vinyl-purpurin-18 methyl ester **4** was then used as a diene for Diels-Alder reaction by reacting with various dienophiles. Thus, reaction of **4** with TCNE in refluxing chloroform for 0.5 h, produced bacteriochlorin **6** (λ max: 762 nm) as a diasteriomeric mixture (7-methyl up or down relative to ring D) in a ratio of 1:2. Yield: 70%.

Reaction of 8-vinyl purpurin-18 **4** with DMAD in refluxing toluene produced Diels-Alder adduct **7** (λ max 780 nm) as a diastereomeric mixture (1:1) in 50% yield. Treatment of **7** with triethyl amine afforded the *trans*- isomer **8** (λ max: 786 nm, yield 80%), while treatment with DBU gave *cis*- isomer **9** (λ max: 795 nm) in 60% yield. The *trans*- isomer **8** on treatment with DBU can also be converted cleanly into *cis*- isomer **9** with less decomposition products. Such results are reported by us and others in preparation of benzoporphyrin derivatives from related vinyl porphyrins.[8, 13] The diastereomeric mixture in isomers **8** and **9** where the methyl group at position-7 and the substituents at position $8^{4'}$ are up or down relative to ring D (*trans*- reduced) were obtained in equal ratio on the basis of NMR and HPLC analyses.

The structures of the newly synthesized compounds were characterized by ^{1}H NMR studies. Vinyl resonances for **4** were observed at δ 7.74 (dd, 1H, J = 18.5, 11.5), 6.01 (dd, 1H, J =18.5) and 5.96 (dd, 1H, J = 11.5), along with three meso protons at δ 9.51, 9.20 and 8.50 ppm. The TCNE adduct **6** was obtained as a diasteriomeric mixture. The NMR resonances for three meso protons and benzoic 8^1 -CH protons were observed at δ 9.00, 8.77, 8.44 and 6.84. The DMAD adduct **7**, also obtained as diasteriomeric mixture and the resonances for meso- and 8^1 -CH protons were in close proximity. The NMR spectrum of the *cis*- isomer **9**, also a diastereomeric mixture shows three sharp meso-peaks (at δ 8.95, 8.30 and 8.18), each was integrating for two protons. In benzobacteriopurpurins **8** and **9**, the 8^1 and 8^2 CH protons were observed at δ 7.63, 7.14 and 7.68, 7.13 respectively. All new compounds were further confirmed by high resolution mass spectrometry.[14]

In summary, we have developed an efficient method for regioselective introduction of vinyl groups in the pyrrole subunit diagonal to the reduced ring of chlorin systems, which on reacting with reactive dienophiles can be converted to a new class of bacteriochlorins (benzobacteriopurpurins). Due to extended conjugation of two exo-cyclic ring, these new bacteriochlorins have near-IR absorptions in the range of 760 to 795 nm.[15] The long wavelength absorption of such bacteriochlorins could make PDT more efficient and more practical because of maximum tissue

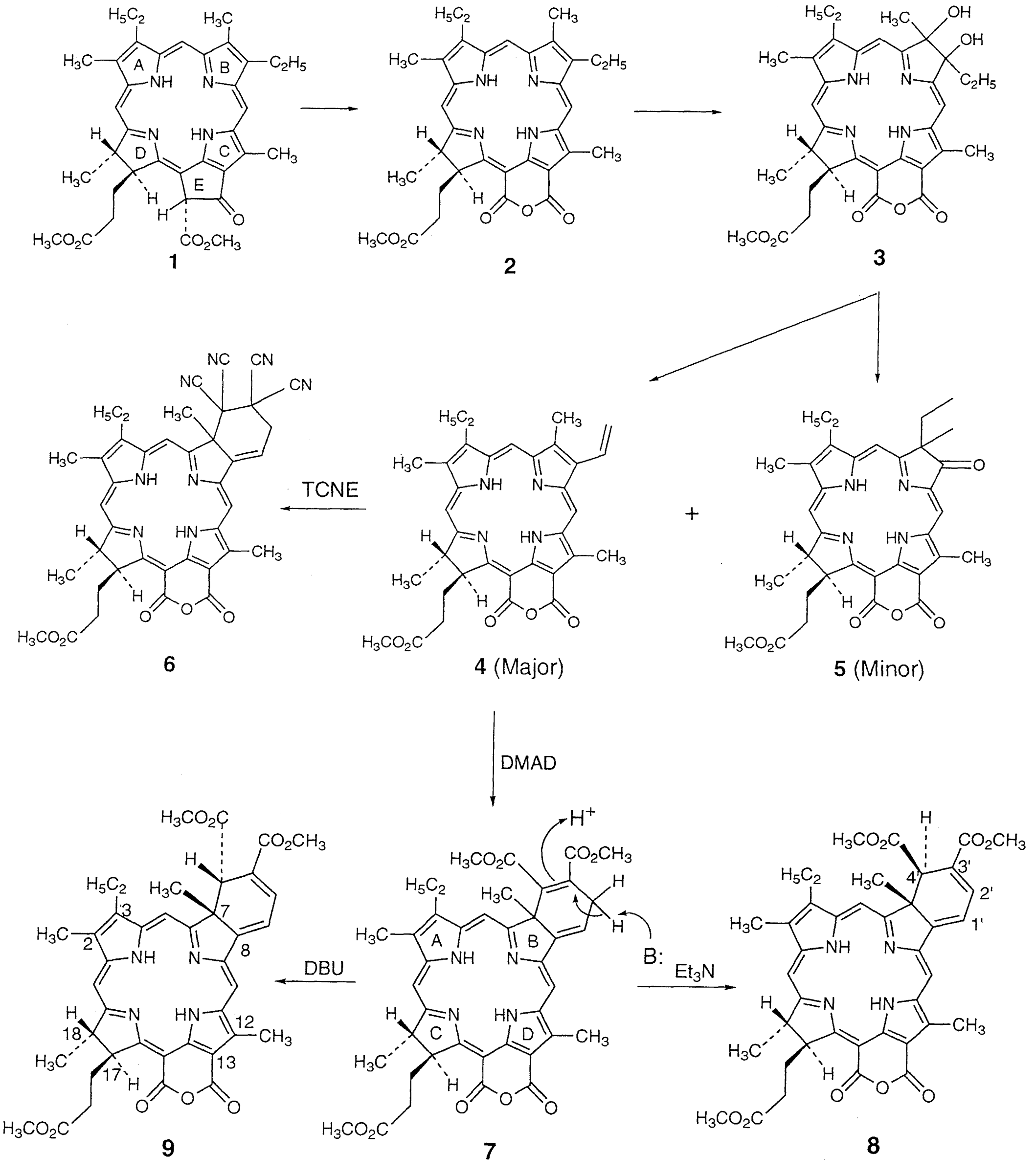

Figure 1. Synthetic approach for the preparation of novel bacteriopurpurins.

penetration and availability of less expensive diode laser in this region. Currently these compounds are being evaluated for their use in PDT, and these results will be published elsewhere.

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14 HRMS of new compounds: **4** ($C_{34}H_{34}N_4O_5$, Calcd: 578.2524, Found: 578.2527); **5** ($C_{34}H_{36}N_4O_6$, Calcd: 596.2635, Found: 596.2610); **6** ($C_{40}H_{34}N_8O_5$, Calcd: 706.2644, Found: 706.2672); **8** ($C_{40}H_{40}N_4O_9$, Calcd: 720.2789, Found: 720.2794) and **9** ($C_{40}H_{40}N_4O_9$, Calcd: 720.2789, Found: 720.2800).
15 Optical spectra: **4** (in CH_2Cl_2) [λ max 420 nm (ε 120000), 507 (11400), 543 (21000), 633 (12500), 684 (43500)]; **8** (*cis*- isomers)[λ max 426 nm (ε 36200), 483 (19600), 536 (11200), 720 (6900), 795 (12300)].