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Impact of peripheral substituents in regioselective synthesis of position-10 or position-20 bromo-bacteriochlorins

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ABSTRACT

Bacteriochlorins derived either from chlorophyll-a or bacteriochlorophyll-a on reacting with pyridinium bromide or N-bromosuccinimide (NBS) gave the corresponding 10- or 20-bromo analogues. In contrast to methyl bacteriopyropheophorbide-a, which afforded 10-bromo derivative, the 7-keto and 8-ketobacteriochlorins under similar reaction conditions gave the corresponding 20-bromo analogues exclusively. In both series, the nature of substituents present at position-3 did not make any difference in the reaction outcome. Density functional calculations were carried out to clarify the difference in reactions outcome. Density functional calculations were carried out to clarify the difference in reactivity of bromination at 10- and 20- *meso* positions.

Halogenated porphyrins and reduced porphyrins (chlorins and bacteriochlorins) have been of significant interest for the preparation of supramolecular structures with defined configuration as models for photosynthetic reaction centres.[1,2] Such tetrapyrrolic systems with variable number of halogen substituents have also been investigated to understand the impact of the type and number of halogen functionalities in altering their electrochemical and photophysical properties.[3–7] Reactions of the halogenated porphyrins, chlorins and bacteriochlorins with a variety of small molecules have shown potential in developing cell-specific photosensitizers for cancer-imaging and photodynamic therapy (PDT).[8] The presence of halogen at the periphery of tetrapyrrolic system also provides an opportunity to introduce a wide variety of functionalities necessary for altering overall lipophilicity, increasing the number of targeting groups and also in developing multifunctional agents for cancer imaging and therapy.[9]

In chlorin systems, e.g., methyl mesopyropheophorbide-*a* **1**, we and others have shown[9,10] that halogen can be selectively introduced at position-20 (i. e., chlorin **2**) due to higher electron density at this particular position, which is next to the reduced ring [the other adjacent position is not available, and is occupied with a fused 5 member isocyclic ring system (ring E)]. However, in ring-B reduced chlorin **3** in which the calculated electron density at position-5 (electron density: −0.316) was slightly higher than position-10 (electron density: −0.311), but gave only 10-bromo analogue **4**, and it could be due to steric hindrance of the substituents present at position-3 of the chlorin moiety.[9] Interestingly, the presence of electron-withdrawing substituents at position-3 in both chlorin and bacteriochlorin systems did not make any difference in selectivity for introducing a bromo- functionality. However, replacing chlorin **1** (ring D reduced) with chlorin **3** (ring B reduced) and bacteriochlorin **5** (rings B and D reduced) as substrates and subjecting them under similar reaction conditions afforded exclusively10-bromo- analogues **4** and **6** respectively (see Schemes 1–3).

For the preparation of 20-bromo bacteriochlorins, we followed two different approaches. In our first approach, the methyl mesopyropheophorbide-*a* **7** was reacted with pyridinium bromide and the corresponding 20-bromo analogue **8** was isolated in 80%

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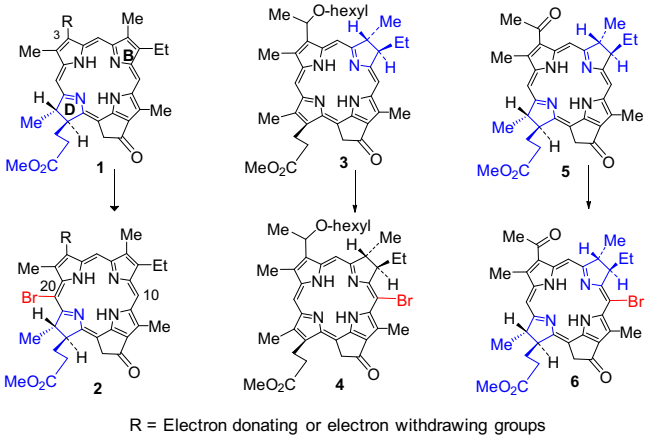
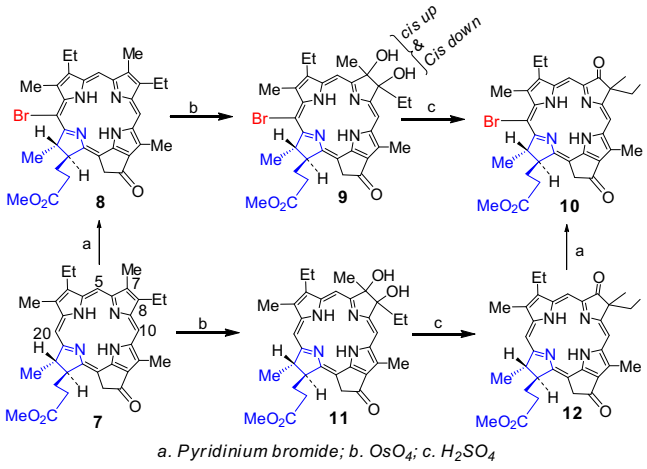
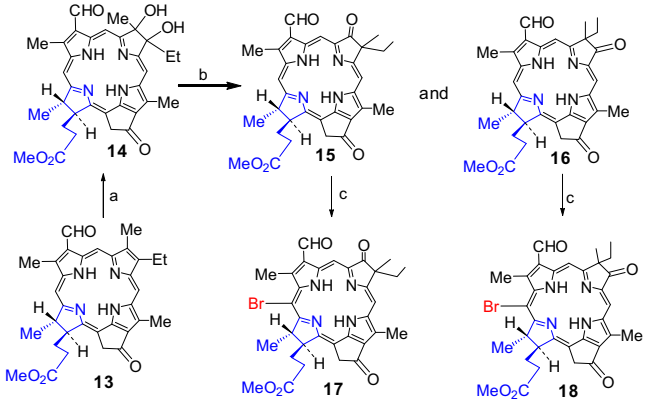


Scheme 1. Regioselective synthesis of bromo-chlorins and bacteriochlorins.

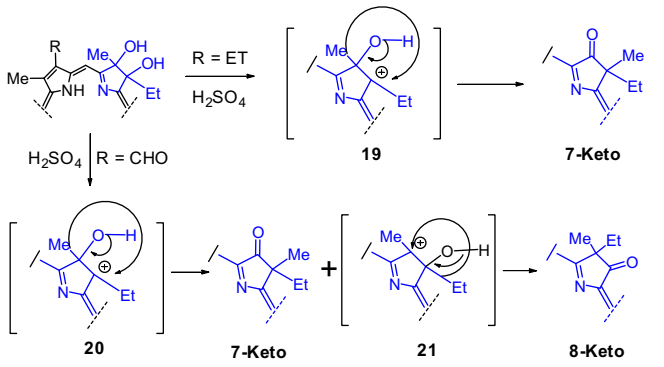


Scheme 2. Synthetic approaches for the preparation of 20-bromo-7-keto-mesopyropheophorbide-*a*.



Scheme 3. Synthetic approaches for the preparation of 20-bromo-3-formyl-7-keto and 8-ketobacteriochlorins.

yield. The intermediate on reacting with osmium tetroxide produced the corresponding bis-hydroxy bacteriochlorin **9**, which on subjecting for Pinacol-Pinacolone reaction conditions produced the desired 20-bromo-7-ketobacteriochlorin **10** in excellent yield. In another approach, the methyl mesopyropheophorbide-a **7** was



Scheme 4. A possible mechanism for the formation of 7- and 8-ketobacteriochlorins.

converted to 7-ketobacteriochlorin **12** by following our well-established methodology,[11] which on reacting with pyridinium bromide or NBS gave 20- bromo-7-ketobacteriochlorin **10** as a sole product.

These results are in contrast to those obtained from bacteriochlorin **5** when subjected under similar reaction conditions, and suggests that the nature of substituents present in periphery makes a remarkable difference in bromo- substitution. To further explore the presence of an electron withdrawing group in the regioselectivity of bromination, 3-formyl-3-devinylpyropheo phorbide a **13** (the ethyl group at position-3 was replaced with a formyl group) was converted to keto-bacteriochlorins **15** and **16**, does not make any difference in the formation of intermediate carbocation **19** (Scheme 4) resulting in the migration of methyl- group over the ethyl under Pinacol-Pinacolone reaction conditions. However, replacing the methyl group with a formyl group at position-3 resulted in the formation of intermediate carbocations **20** and **21** (Scheme 4) in which preferential migration of either methyl- or ethyl group produced an isomeric mixture of ketobacteriochlorins **17** and 1**8**, which under bromination conditions also gave the corresponding 20-bromo analogues **17** and **18** respectively. These results further suggest that the nature of substituents at position-3 in both 7- and 8-ketobacteriochlorin did not make any difference in regioselective outcome of the brominated products.

The formation of 7-keto-bacteriochlorin **10** from the corresponding *vic*-dihydroxybacteriochlorins **9** and **11** clearly indicates that the presence of bromo-functionality at position-20 does not make any difference in the preferential migration of the methyl group over the ethyl functionality under Pinacol-Pinacolone reaction conditions.

The presence of a bromo- functionality at position-20 of ketobacteriochlorins **10**, **17** and **18** was confirmed by detailed NMR study. The full assignment of the 1D proton NMR spectra was aided by correlations obtained from 2D ^{1}H COSY and NOESY spectra. The COSY spectra were used to obtain through-bond correlations that sort the proton signals into separate spin systems. NOESY cross peaks were used to make specific assignments of individual proton signals based on their proximity to neighbouring protons. This approach was used to obtain the complete ^{1}H NMR assignment of the three ketobacteriochlorins (see "Supporting Material" information).

Substitution at position-20 is indicated because no *meso* proton signal could be assigned to that site. The two *meso* proton signals observed for each of the three ketobacteriochlorins were clearly and unambiguously assigned to H-5 and H-10. H-5 was identified by NOESY cross peaks correlated with the protons of the 3-CH_2CH_3, 3-formyl, 7-CH_3 and 7-CH_2CH_3 groups. Similarly, H-10 was identified by NOESY cross peaks correlated with the protons of the 8-CH_3, 8-CH_2CH_3 and 12-CH_3 groups. None of these *meso*