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A Novel and Convenient Conversion of Chlorins to Phytoporphyrins During the Modification of Chlorophyll Derivatives

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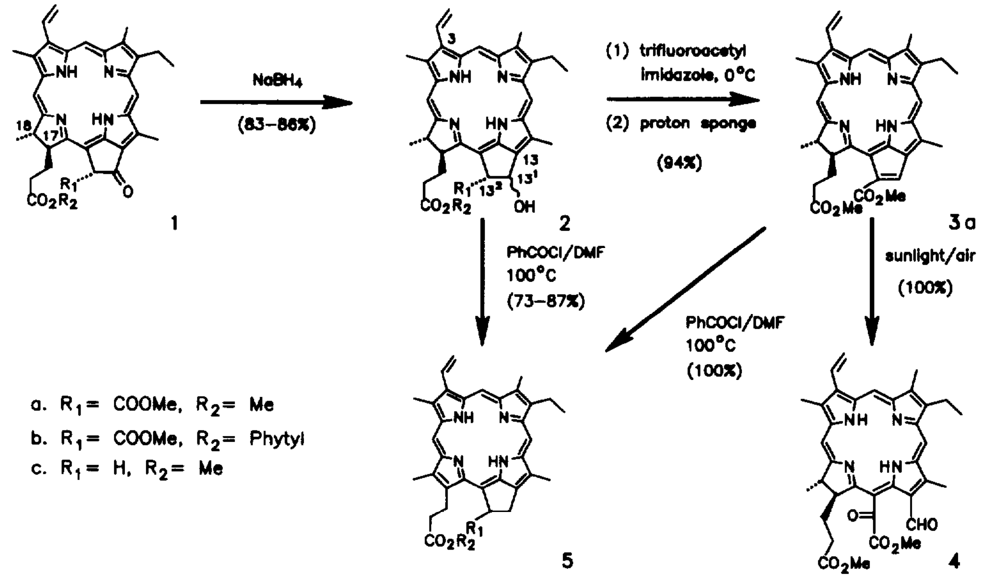
Abstract: Chlorophyll derivatives **2a**, **2b**, **2c** and **3** have been readily converted to their corresponding phytoporphyrins **5a**, **5b**, **5c** in excellent yields using benzoyl chloride in DMF. This method affords a new and efficient route to prepare monovinyl porphyrins which can be used as intermediates for the further preparation of chlorophyll related petroporphyrins and regiochemically pure benzoporphyrin derivatives for use in photodynamic therapy.

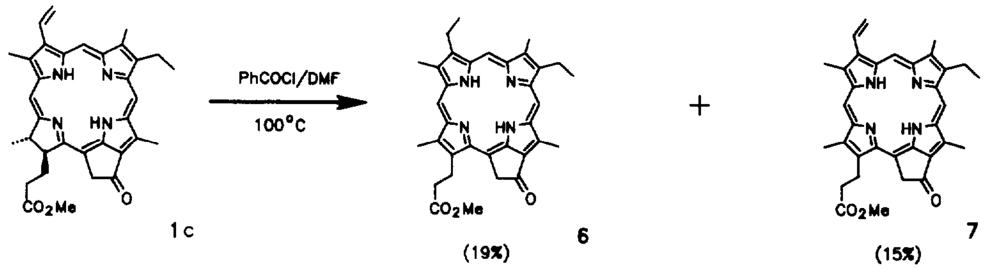
Hydrogen iodide in glacial acetic acid, which can be used for the conversion of 3-vinyl chlorins to 3-ethyl porphyrins via tautomerization of the exocyclic double bond, served as an important reagent in the elucidation of the chlorophyll structure.[1] This reaction, termed the "HI reduction" or "HI isomerization" by Hans Fischer, was a convenient method for the preparation of chlorophyll related porphyrins (i.e. phytoporphyrins).[2] However, the reaction mechanism, involving isomerization and migration of hydrogens at positions 17, 18 to the exocyclic 3-vinyl group, remains obscure. Although a carbocation rearrangement mechanism has been recently suggested by Hynninen,[3] the harsh acidic conditions and the complex product distribution have made mechanistic studies difficult. We describe here a new method for the conversion of chlorins into phytoporphyrins which may help to elucidate this reaction mechanism, especially the acid-catalysed migration of H atoms at postions 17, 18. This new method can also be used as an efficient route to prepare monovinyl porphyrins from chlorophyll derivatives.

During our studies on natural antioxidant chlorins we prepared a series of chlorins having specific exocyclic rings.[4,5] Of these chlorins 13^1-deoxo-13^1,13^2-dehydropheophorbide *a* methyl ester (**3c**) was prepared by the dehydration of 13^1-deoxo-13^1-hydroxypheophorbide *a* methyl ester (**2a**), a diastereomeric mixture which was originally obtained from $NaBH_4$ reduction of pheophorbide *a* methyl ester (**1a**).[6] Although **3a** (m.p. > 300°C) has high thermal stability, we found that it is extremely photosensitive and



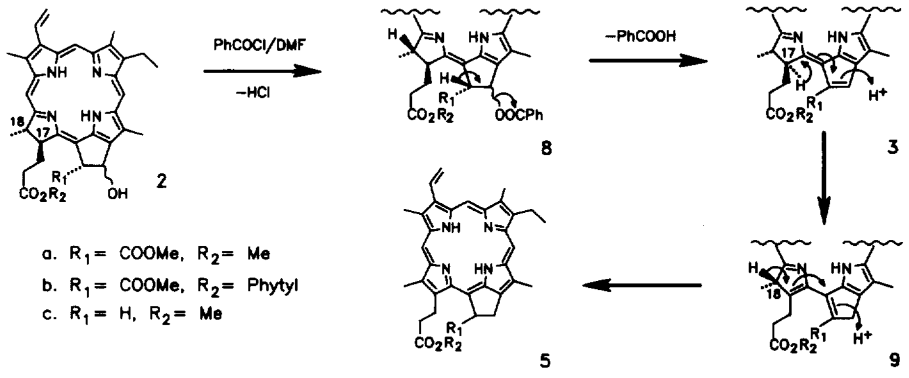
reaction in air with sunlight oxidatively cleaved the 13^1-13^2 double bond in its exocyclic ring to quantitatively give vinylpurpurin **4** while the 3-vinyl group remained unchanged. Thus formation of a 13^1-13^2 double bond in the exocyclic ring of **3c** significantly perturbs the π electronic structure of the chlorin macrocycle and an acid catalyzed isomerization of this double bond should, we felt, bring about the conversion of **3a** into the more stable porphyrin product **5a**.

We found that benzoyl chloride in DMF, which significantly reduces side-reactions, is a much milder reagent than HI in acetic acid to achieve this transformation. Reaction of **3a** with 1 equiv of benzoyl chloride in DMF at 100°C for 20 min, gave phytoporphyrin **5a** in quantitative yield. With this promising finding, we expanded our procedure to hydroxychlorin **2a**, which, after reaction under the above conditions for 45 min, gave the same product **5a** in 87% yield. Similarly, the conversion of the two hydroxychlorins **2b** and **2c** gave **5b** and **5c** in 81% and 73% yield.



When the above procedure was applied directly to the 3-vinylchlorin, pyropheophorbide *a* methyl ester (**1c**), a mixture of phytoporphytin methyl ester **6** (19% yield) and 3-vinylphytoporphyrin methyl ester **7** (15% yield) was obtained, with recovery of 40% of the starting material **1c**. The formation of the non-isomerized (oxidized) product **7** is probably due to direct autoxidation under the acidic reaction conditions.

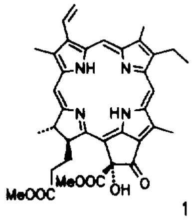
A possible isomerization mechanism is presented in Scheme 1. The formation of phytoporphyrin **5** from hydroxychlorin **2** can be regarded as an acid-catalyzed double isomerization of the intermediate **3**, which itself is formed by elimination of a molecule of benzoic acid from the initial benzoate **8**. Migration of the proton at position 17, with relief of the steric strain in the intermediate **3**, gives intermediate **9** which subsequently tautomerizes, with the loss of a proton at position 18, to give the fully conjugated product **5**.



a. R_1 = COOMe, R_2 = Me
b. R_1 = COOMe, R_2 = Phytyl
c. R_1 = H, R_2 = Me

Scheme 1

Water present in the reaction medium will quench the carbocation intermediates and generate side products or cause decomposition. This was also observed in the transformation of polyhydroxychlorins. For example, the reaction of benzoyl chloride (2 equiv) with the diastereomeric diol **11**, obtained from the NaBH$_4$ reduction of 13^{2}R-hydroxypheophorbide *a* methyl ester (**10**),[7] gave a 2% yield of **1a** and a unidentified mixture of porphyrins. Similarly, the diastereomeric triol **12**, prepared from the LiAlH$_4$ reduction of pheophorbide *a* methyl ester (**1a**), also afforded a complicated porphyrin mixture.



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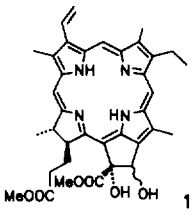

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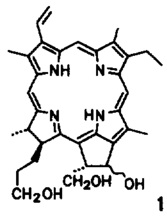
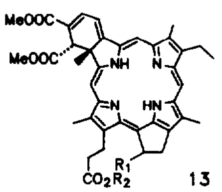


12

For the preparation of chlorophyll related 3-vinylporphyrins, the present methodology has definite synthetic advantage over the previously reported method.[8] Diels-Alder reaction of the monovinylporphyrins

5 with dimethyl acetylenedicarboxylate followed by DBU-promoted rearrangement of the cycloadducts gave 32-36% yields of **13**, a new class of regiochemically pure benzoporphyrin derivatives, which can act as photosensitizers in the photodynamic therapy of tumors.

Deoxophylloerythroetioporphyrin **14**,[9,10] an important chromatographic reference compound in geochemistry, has also been prepared (67-75% yield) in a one-pot procedure which involved reduction of vinyl to ethyl and the subsequent decarboxylation by heating in 1,5,7-triazabicyclo[4,4,0]dec-7-ene. The carboxylic acids were obtained from the alkaline or acidic hydrolysis of the phytoporphyrins **5a**, **5b** and **5c**.



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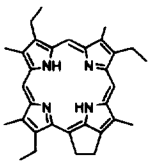

14

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