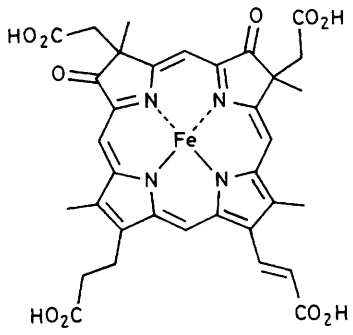
Differentiation of Bacteriochlorin and Isobacteriochlorin Formation by Metallation. High Yield Synthesis of Porphyrindiones *via* OsO_4 Oxidation

Chi K. Chang,* Chariklia Sotiriou, and Weishih Wu

Department of Chemistry, Michigan State University, East Lansing, MI 48824, U.S.A.

Zinc oxochlorins (porphyrinones) react with osmium tetroxide to give exclusively adjacent-ring saturated isobacteriochlorins without any bacteriochlorins that would normally arise from such a reaction with free base porphyrinones; the diols can be converted into the haem d_1-like porphyrindiones.

The recent discovery that the green coloured d_1 haem prosthetic group present in cytochrome cd has a dioxoisobacteriochlorin (acryloporphyrindione) structure (**1**) has generated much interest in these unusual porphyrin quinones.[1—3] The only method known to date for the synthesis of such compounds is the hydrogen peroxide–sulphuric acid oxidation of β-substituted porphyrins resulting in a complex mixture of isomeric products containing one, two, and three oxo groups on the ring with uniformly poor yields.[4,5] The oxochlorins, such as (**2a**), can be prepared with a significantly higher yield



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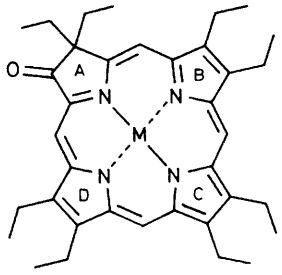
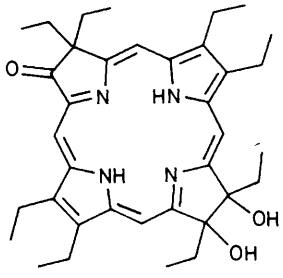


(2) a; M = 2H
b; M = Zn



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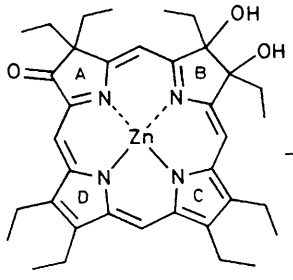

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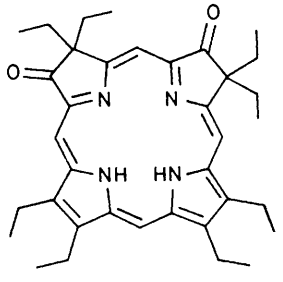

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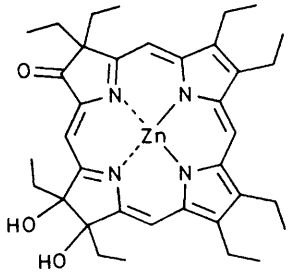

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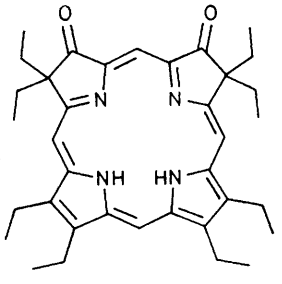
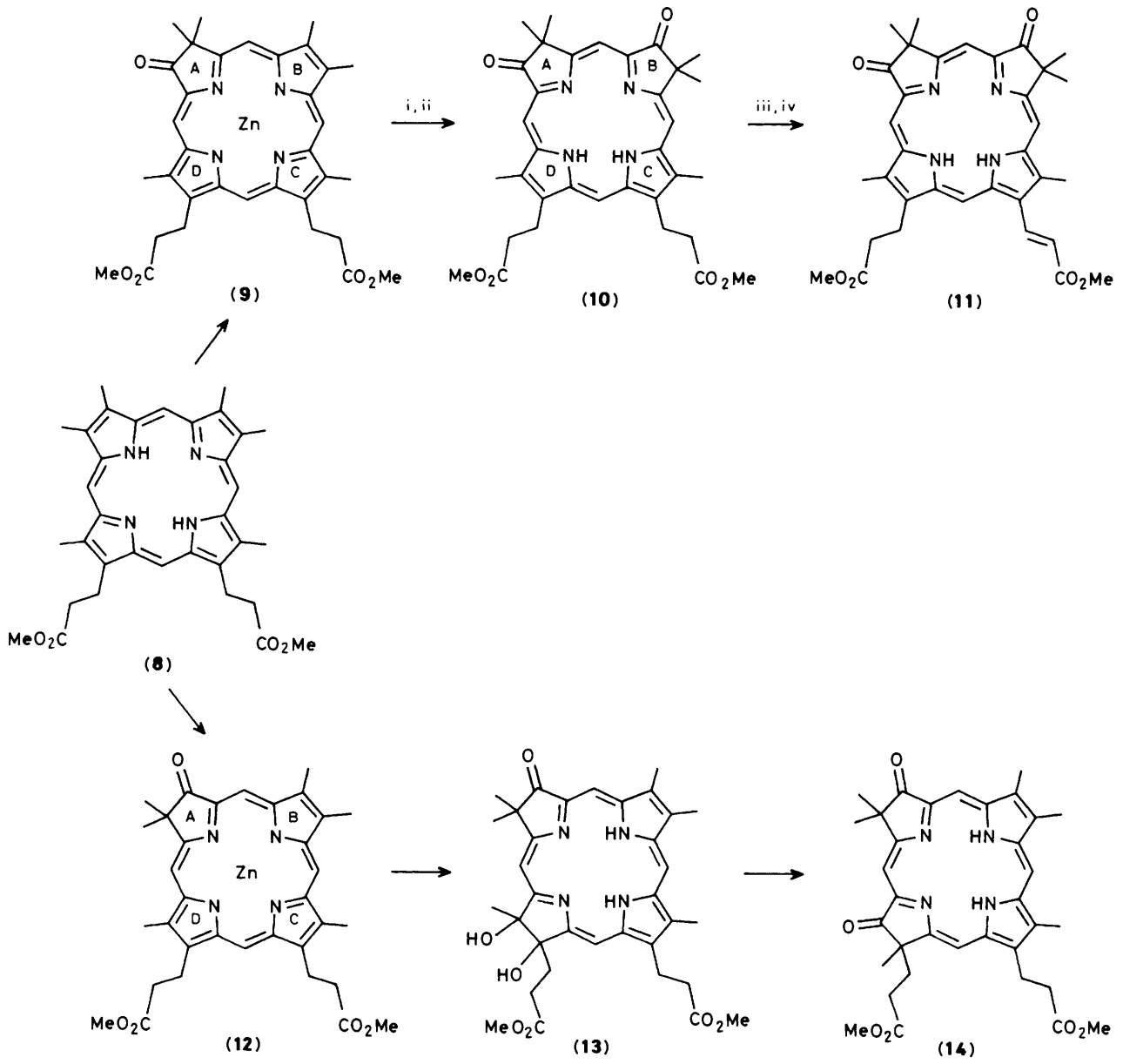


(7)

by an alternative 2-step reaction *via* OsO_4 oxidation and acid catalysed pinacolic rearrangement.[6,7] Unfortunately, further oxidation of (**2a**) by OsO_4 invariably leads to the bacteriochlorin (**3**),[4] which upon rearrangement gives two isomeric dioxobacteriochlorins (porphyrin-2,12- and -2,13-diones).

We report here that the OsO_4 addition preference can be altered dramatically in favour of the isobacteriochlorin formation simply by metallation of the ring. The zinc complex (**2b**) was found to react with OsO_4 (1.5 equiv.) in CH_2Cl_2 containing 1% pyridine to give predominantly (**4**) (>60% yield) which can be treated with sulphuric acid to give (**5**). A small amount of the ring D diol (**6**) was also obtained which rearranged to yield about equally (**5**) and (**7**). If the synthetic goal is (**5**), the crude dihydroxylation product can be used directly in the pinacol rearrangement as the ratio of (**5**) : (**7**) is usually greater than 30. That the osmate addition mainly occurred at ring B (**4**) is possibly due to the electron withdrawing effect of the carbonyl group rendering the adjacent ring D double bond less reactive. It is also noteworthy that during the pinacol rearrangement of (**4**) or its free base, none of the possible porphyrin-2,8-dione was observed. Insertion of other metal ions such as Cu^{II} and Ni^{II} has the same effect of switching the osmate addition pattern but the yields of osmate esters were less satisfactory. The remarkable alteration of site of attack by metallation in the chlorin system appears to be a general phenomenon. Previously it has been observed that the diimide reduction of free base tetraphenylchlorin (TPC) produces only tetraphenylbacteriochlorin whereas Zn^{II}TPC gives exclusively Zn^{II} tetraphenylisobacteriochlorin.[8] Similarly, reduction of the Ni^{II} pheophorbide family of chlorins by Raney nickel promotes the formation of isobacteriochlorins.[9] Whitlock and Oester suggested that the saturation of a diametrical pyrrole double bond in the free base chlorin may be prompted by the diagonal π-electron delocalization pathway that bypasses the outer β–β′ bonds of the pyrroline ring and its opposite partner, leading to the bacteriochlorin formation with minimum loss of π-energy.[8,10] The preference for this valence tautomer would be diminished when the system becomes metallated or protonated. This hypothesis did not explain why the double bond saturation occurs *exclusively* at the adjacent ring in the metal complex since one would expect that the absence of a preferred π-delocalizing pattern only favours a more random attack. Neither did previous MO calculations of ZnTPC show a significant difference in π-electron density between the opposite and the adjacent β–β′ double bonds.[10] Presently, extended Hückel calculations are being undertaken on the metalloporphyrinone system using the newly acquired crystal structure parameters of Ni^{II} (**2a**);[11] it is hoped that the refined calculations may uncover clues to explain this phenomenon.

The selective saturation of the porphyrinone double bonds has made possible the synthesis of a variety of porphyrin-2,7-diones with side chains at specific positions. For example, the stereochemically uncomplicated dione (**10**) and its acrylic derivative (**11**), either in solution or in a reconstituted protein environment, proved to be accurate model compounds and spectral probes for d_1 haem. The dione (**10**) could be prepared by the H_2O_2–H_2SO_4 oxidation of (**8**), with a <2% yield after tedious separations from a mixture of no less than 10 oxo products.[12] With the zinc method, (**10**) was prepared from (**9**)[7] cleanly with a high yield (Scheme 1), and the unreacted starting material in the OsO_4 oxidation of (**8**) and (**9**) could always be recovered for recycling. The intermediacy of the porphyrinone (**9**) seems necessary. Attempts to react the Zn complex of (**8**) or Zn^{II} octaethylporphyrin directly with an excess of OsO_4 have only resulted in intractable pigments. The two-stage oxidation *via* isolated porphyrinone has also imparted a higher degree of regioselectivity for the isobacteriochlorin-type porphyrindione formation. In the present study, if the isomeric (**12**)[7] is used, the major product is (**13**), despite the overwhelming steric advantage for OsO_4 to attack ring B. With porphyrin (**8**), the osmate selectivity of ring B (or A) *vs.* D is 37 : 8.[7] The pinacolic rearrangement product from (**13**) is exclusively (**14**), apparently reversing the migratory aptitude of methyl < propionate observed in simple *vic*-dihydroxychlorins[13] but fully agreeing with the above observation of porphyrinone diols.



Scheme 1. i, OsO_4, H_2S, 65%; ii, conc. H_2SO_4, 95%; iii, OsO_4, H_2S, 60%; iv, HCl–dioxane–H_2O, conc. H_2SO_4–MeOH, 85%.

Further reaction of free base (**10**) with 1.2 equiv. of OsO_4 resulted in exclusively a ring c diol, presumably for the same reason cited above for (**4**): to avoid the carbonyl group next to ring D. Heating the diol in dilute hydrochloric acid triggered an elimination of H_2O and yielded a β-hydroxy propionate which eliminates further to give the acrylate (**11**), following a procedure similar to our recent synthesis of a d_1 analogue.[2] The visible spectrum of (**11**) [in $CHCl_3$, 661 nm (ε 15 400 dm^3 mol^{-1} cm^{-1}), 611 (25 000), 568 (14 000), 446 (66 000), 423 (93 000)] is again indistinguishable from that of the isolated d_1 pigment from cytochrome cd of *Pseudomonas aeruginosa*.[14]

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