Synthetic Routes to C-Methylated Chlorins

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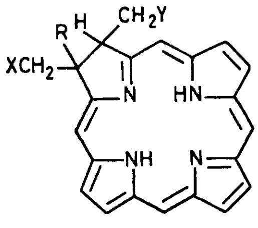
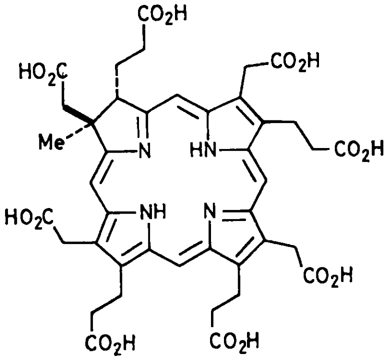
Summary The chemistry of nitroalkanes has been used to develop two rational synthetic routes to the new class of *C*-methylated chlorins.

CHLORINS have been of great interest from the time the structures of chlorophylls a and b were elucidated; such chlorins carry two vicinal hydrogen atoms on the reduced ring [*cf.* (**1**), R = H]. Recently, a new class of chlorins has been discovered of which Faktor I[1] (**2**) and bonellin[2] (**3**) are examples; here dehydrogenation of the reduced ring is blocked by *C*-methylation [*cf.* (**1**), R = Me]. We now outline two routes for the rational synthesis of such *C*-methylated chlorins.



(1)



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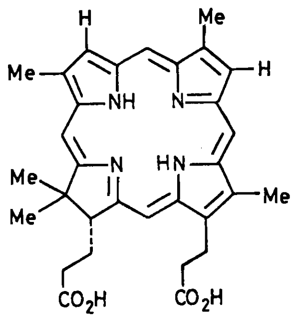
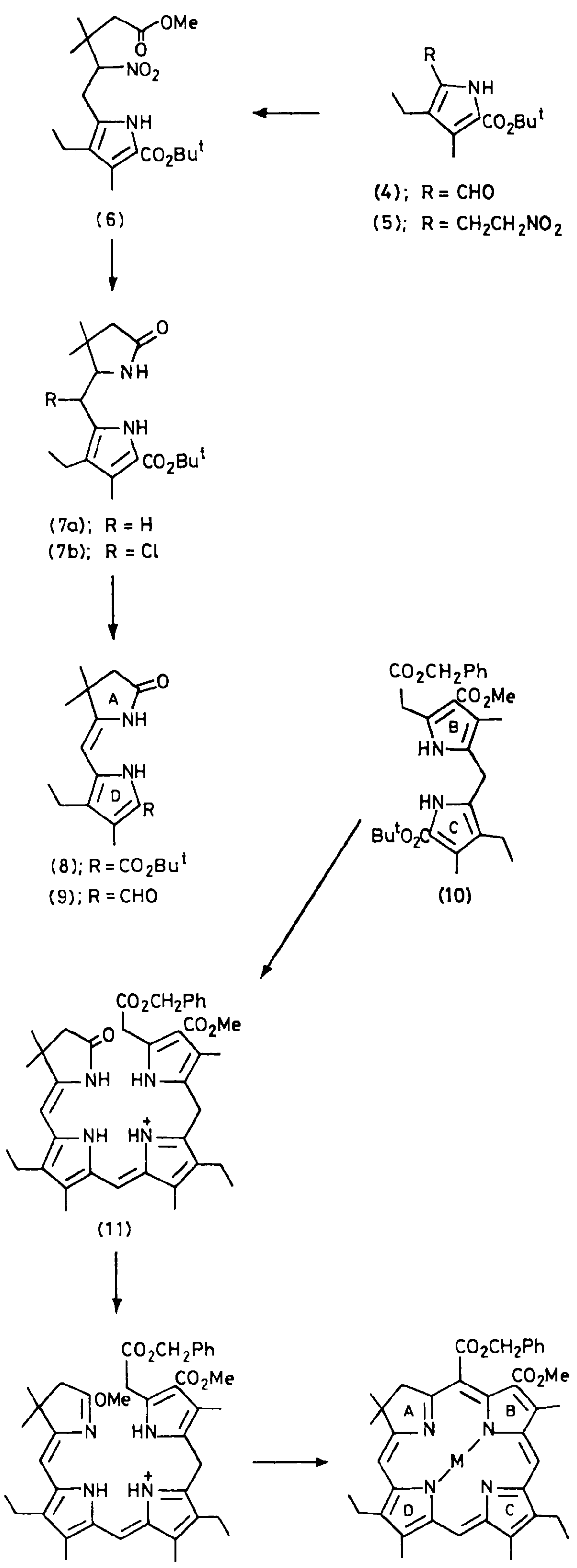


(3)

For the first approach, the western A–D component was constructed from the aldehyde (**4**) by condensation with nitromethane followed by borohydride reduction to give (**5**)† which underwent Michael addition, catalysed by $Bu_4N^+F^-$, to methyl 3-methylbut-2-enoate forming the ester (**6**)† (65% yield). Reduction, first with zinc and acetic acid, then with titanium(III) chloride yielded the lactam (**7a**)† (94%). This, by controlled treatment with Bu^tOCl, gave the chloride (**7b**) which was hydrolysed and dehydrated to give the unsaturated lactam (**8**)† (67%). The *Z*-configuration was established by *X*-ray analysis by Dr. P. Raithby.[3] Methyl orthoformate and trifluoroacetic acid (TFA) then converted[4] (**8**) into the required aldehyde (**9**)† (86%).



(4); R = CHO
(5); R = $CH_2CH_2NO_2$

(6)

(7a); R = H
(7b); R = Cl

(8); R = CO_2Bu^t
(9); R = CHO

(10)

(11)

(12)

(13); M = Cu^{II}
(14); M = H, H

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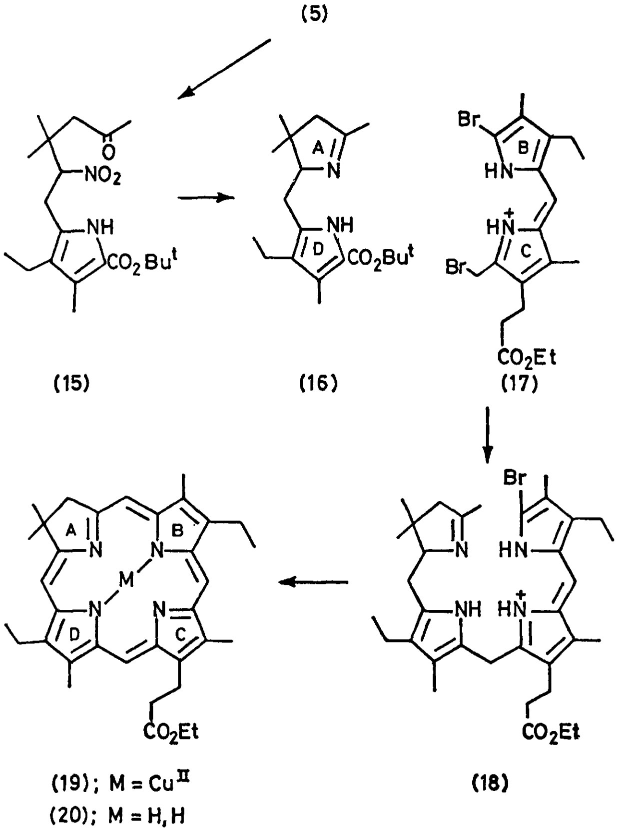
† Fully characterised new compound.

Synthesis of the eastern B–C component (**10**) followed a standard pyrromethane approach and when the t-butyl ester (**10**) was cleaved by TFA followed by addition of the A–D component (**9**), condensation occurred to generate the linear tetrapyrrole derivative (**11**) (76%). Ring closure of this product was achieved by conversion with $Me_3O^+BF_4^-$ into the imino-ether (**12**) (77%), which with copper(II) acetate in hot acetonitrile gave the *C*-methylated chlorin as its Cu^{II} complex (**13**). Copper was removed by TFA saturated with hydrogen sulphide (a valuable reagent which seems to be novel) to give the desired macrocycle (**14**)†, M^+ 630 ($C_{39}H_{42}N_4O_4$ requires 630); the overall yield for the final steps was 7·4%.



An alternative approach involved fluoride-catalysed Michael addition of the nitroethylpyrrole (**5**) to mesityl oxide and the resultant ketone (**15**)† (88%) was reduced as above for (**6**) to yield the pyrroline (**16**)† (88%) which served as the western A–D component. It was converted into the corresponding α-free pyrrole by TFA and this reacted readily with the eastern component, a dibromopyrromethene[5] (**17**) (readily prepared by standard methods), to form the linear tetrapyrrole derivative (**18**). The product was characterised by n.m.r. spectroscopy then immediately ring-closed with copper(II) acetate in acetonitrile to give the *C*-methylated chlorin (**19**) (6·8%). Demetallation of the complex was carried out as above and the product (**20**)† (71%) showed M^+ 538·3319 ($C_{34}H_{42}N_4O_2$ requires 538·3308).

Optimisation of the ring-closure steps is in progress but the simplicity of these rational routes, especially the second, means that their application to synthesis of such natural products as (**3**) is already practicable.

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