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Locked π-Expanded Chlorins in Two Steps from Simple Tetraarylporphyrins

Julien Fouchet, Christophe Jeandon, Romain Ruppert, and Henry J. Callot*

U.M.R. 7177 du C.N.R.S., Faculté de Chimie, Université Louis Pasteur,
1, Rue Blaise Pascal, F-67000 Strasbourg, France

callot@chimie.u-strasbg.fr

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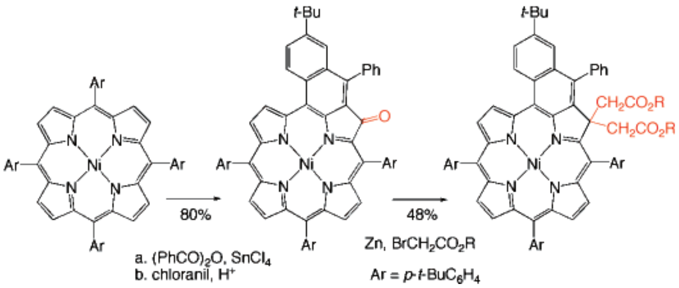
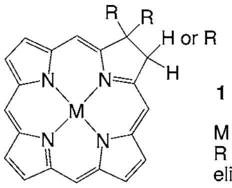
ABSTRACT



Upon tandem Reformatsky reaction, easily accessible porphyrinic ketones give “locked” chlorinic diester. Both ketones and diesters, as bases or palladium complexes, efficiently generate singlet dioxygen, as demonstrated by trapping with cholesterol.

Whether as photosensitizers for photodynamic therapy or as building blocks for models of photosynthetic systems, chlorins (β,β'-dihydroporphyrins) are often chosen since their chromophores show intense long wavelength absorptions ($\geq$600 nm).[1] These compounds are accessible by modifications of natural products and chlorophylls or by total synthesis. Whatever the route selected, the stability of the products vs. β,β'-dehydrogenation or -elimination to form more stable porphyrins is crucial. In recent years several routes to “locked” chlorins (general structure **1**) have been developed, the most recent and efficient one by Gryko and Galezowski.[2−6] The prerequisites for an optimal photosensitizer are (a) efficient generation of singlet oxygen, (b) significant absorption at wavelengths $\geq$600 nm, (c) easy access (limited number of good yield steps, simple reaction conditions, minimal number of chromatographic separations, easy scaling up, cheap reagents), (d) chemical stability (locked β positions), (e) photochemical stability above 600 nm, and (f) functional groups that are not conjugated to the chromophore and that can be easily modified in order to tune the hydro- or lipophilicity of the photosensitizer.



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M = H$_2$ or metal ion
R = any group that cannot participate in an elimination or dehydrogenation reaction

Figure 1.

In this letter we present a shorter and more economical route to such chlorins, as well as tests demonstrating that our chromophores and some of their metal complexes act as stable and efficient photosensitizers to produce singlet oxygen.

During the study of the benzoylation of nickel tetraarylporphyrins, we showed that **Ni-2** (as well as the *p*-OEt

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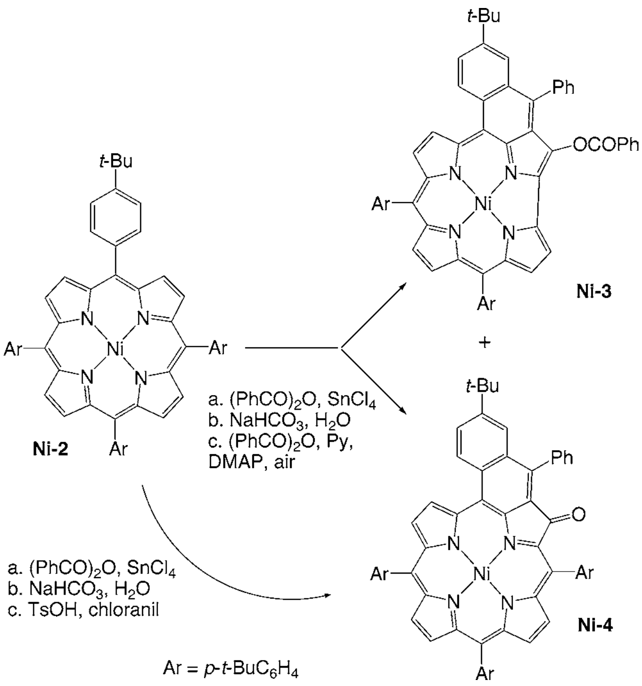
analogue),[7] instead of yielding the expected benzoylporphyrin, gave, after oxidation under basic conditions, corrole **Ni-3** (up to 24%) and ketone **Ni-4** (up to 35%). To synthesize precursors of corrole **Ni-3** and widen the scope of the ring contraction,[8] we wished to (a) optimize the yield of ketone **Ni-4** at the expense of corrole **Ni-3** and other byproducts and (b) introduce an acetic acid side chain where the carbonyl group was initially located in ketone **Ni-4**.

Scheme 1



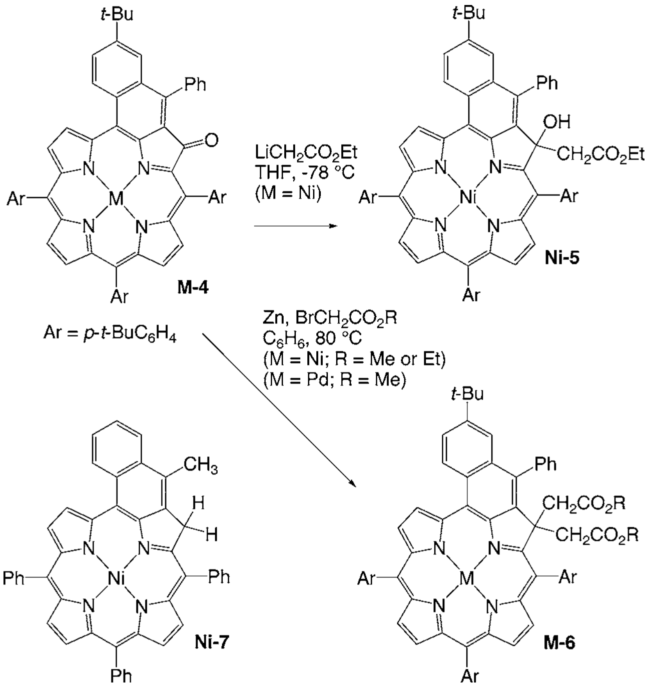
The first target was reached when we found that ketone **Ni-4** could be produced as the only product of low polarity in 80% yield from the corresponding porphyrin under acylating, then oxidizing conditions. The presence of acid allowed the isomerization of the initial tertiary alcohol produced by the acylation + cyclization sequence, thus ensuring the full transformation of the product to ketone **Ni-4** via the pyrrolic secondary alcohol. Under the same conditions the corresponding palladium complex **Pd-2** gave ketone **Pd-4** in 79% yield.

To perform the next step, the Reformatsky reaction was selected, but instead of hydroxyester **Ni-5**, diester **Ni-6**, a product of a double Reformatsky reaction, was obtained in 48% and 40% yield (ethyl and methyl esters, respectively). Independently, reaction of ketone **Ni-4** with the anion of ethyl acetate at −78 °C gave hydroxyester **Ni-5** in nearly quantitative yield.

The structure of diesters **Ni-5** and **Ni-6** was unambiguously established from their UV−visible and NMR data. The UV−visible spectrum of **Ni-6** (R = Me) shows two major absorption bands: a Soret band at 450 nm and an intense absorption at 668 nm as one would expect for a chlorin. However, due to the extended conjugated system, both bands show a bathochromic shift relative to simple *meso*-tetraarylchlorins whose corresponding bands are located in the 615−620 nm range. Similar chlorins bearing an additional unsaturated ring have been described[9,10] and also showed a bathochromic shift (670 nm for the longest wavelength band of **Ni-7**[10]).

The NMR data for **Ni-6** (R = Me) are in full agreement with the proposed structure: the two acetic chains show the expected singlet for the methyl groups and an AB system for the diastereotopic methylenic protons. On the other hand, hydroxyester **Ni-5** (R = Et), while showing an almost identical UV−visible spectrum, gave unequivocal NMR data for the side chain (two pairs of diastereotopic protons) as well as an exchangeable signal for the hydroxyl proton. For **Ni-5** as well as for all diesters, the signals for methyl and ethyl protons are shifted to high field as one would expect for groups placed between two aromatic rings.

Scheme 2



Examples of tandem Reformatsky reactions forming gem C−C bonds are scarce[11] and are, to our knowledge, only

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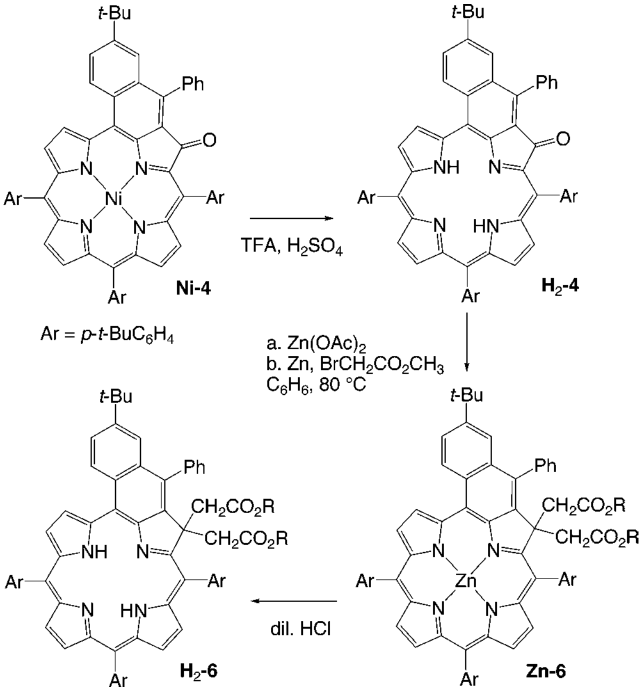
known for substrates whose reactive positions are at the carboxylic acid oxidation level (nitriles, acid chlorides, ortho esters, or formates).

In our case, we suggest that a hydroxyester (as a zinc alcoholate) was formed initially, but that the loss of the oxygenated group was facilitated by both the zinc ion and the stability of the resulting cation, which in turn reacted with excess reagent. We checked that, under acidic conditions (TsOH in CH_2Cl_2), hydroxyester **Ni-5** produced easily the corresponding cation (λ_{max} = 407 nm (ϵ = 33 000), 499 (21 500), 720 (10 000), 792 (9 800), 875 (10 600). Such long wavelength absorptions, extending to the near-infrared region, are known for cations generated on a carbon directly bound to the porphyrin ring.[12]

We also checked the reactivity of ketones lacking the phenyl ring on the additional six-membered ring[9] but obtained only untractable mixtures under Reformatsky conditions.

To extend the scope of the reaction to other metal complexes and the corresponding bases, we first subjected ketone **Pd-4** to the Reformatsky conditions and obtained diester **Pd-6** in 24% yield. To obtain the corresponding base we could not start with **Ni-6**, whose attempted acid-catalyzed demetalation led to extensive decomposition. We demetalated ketone **Ni-4** in TFA-H_2SO_4 (95% yield) and remetalated the resulting base **H_2-4** with zinc(II) (Scheme 3). This complex was then subjected to the Reformatsky conditions and gave diester **Zn-6** in 20% yield. Acid treatment of **Zn-6** gave base **H_2-6**.

Scheme 3



Although sterically hindered by two neighboring aryl rings, the two ester groups of **Pd-6** could be easily hydrolyzed by sodium hydroxyde in *n*-propanol into the dicarboxylic acid. In turn this diacid could be esterified back to **Pd-6** in acidic methanol.

All new compounds possessing long wavelength absorptions (see examples in Figure 2) were tested under illumination (λ > 510 nm, to avoid excitation in the Soret band region) in order to check their ability to generate singlet oxygen.

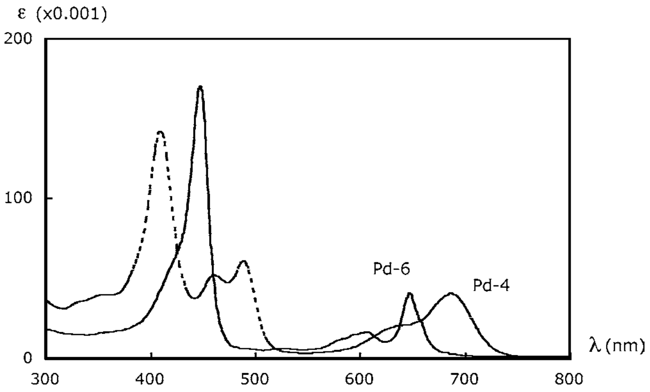
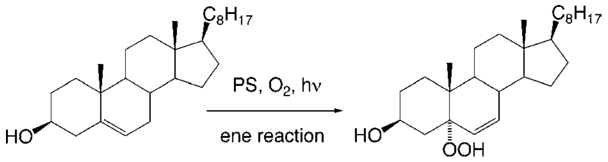


Figure 2. UV−visible spectra of **Pd-4** and **Pd-6**.

Many spectroscopic or chemical methods of singlet oxygen detection are available. Among them, the oxidation of cholesterol is well documented,[13] used as detector for singlet oxygen in biological systems,[14] and very easy to carry out (see the Supporting Information for experimental details).

Scheme 4



The results are collected in Table 1. For comparison, the corresponding *meso*-tetraarylporphyrin base **H_2-2** was tested under the same experimental conditions. As expected, ketone

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Table 1. Cholesterol Photochemical Oxidations[a]

photosensitizer (PS)	longest wavelength band (λ_{max} and ϵ in C_6H_6)	turnover no. (after 3 h of irradiation)
H_2-2	648 (3400)	9
Ni-6 (R = Me)	668 (14000)	0
Zn-6	670 (25000)	0
H_2-4	724 (26000)	27
H_2-6	686 (27000)	2.5
Pd-4	686 (40000)	35
Pd-6	648 (40000)	38

[a] Experimental conditions: 20 mL of benzene, cholesterol (2×10^{-3} mol/L), PS (10^{-5} mol/L), 3 h of irradiation (250 W slide projector bulb, $\lambda > 510$ nm), cholesterol/PS = 200.

Ni-4 and chlorin **Ni-6** (R = Me) were photochemically inactive, but both were recovered intact after irradiation. No cholesterol oxidation products were detected in the presence of zinc complexes **Zn-4** and **Zn-6** (R = Me), but each one was converted cleanly in one single compound. Full characterization of both compounds is still under way, but mass spectroscopic analysis showed that these oxidized compounds are the zinc complexes of products resulting from the oxidative cleavage of the tetrapyrrole ring. Both bases **H_2-4** and **H_2-6** and palladium complexes **Pd-4** and **Pd-6** were found to be active and stable under irradiation conditions, as shown by the fact that their electronic spectrum taken after irradiation was superimposable with the starting spectrum. **H_2-6**, **Pd-4**, and **Pd-6** are excellent photosensitizers when compared to porphyrin base **H_2-2**: compare entry 1 (9 turnovers in 3 h) and entries 4, 6, and 7 (from 27 to 38 turnovers in 3 h). Ketone **Pd-4** was recovered unchanged even after long-term irradiation (10 h and more than 100 turnovers).

This reaction sequence represents by far the shortest and most efficient route to locked chlorins that are good photosensitizers since (a) ketones **Ni-4** and **Pd-4** were prepared in 80% and 79% in a one-pot sequence from a nickel or palladium tetra-*p*-*tert*-butylphenylporphyrin, itself made in a one-pot sequence from pyrrole and *p*-*tert*-butylbenzaldehyde in 23% yield, and transformed into **Ni-6** and **Pd-6** in one step, via a novel tandem Reformatsky reaction, (b) the overall yields of diesters **M-6** from shelf chemicals are 8.9% (M = Ni) and 4.5% (M = Pd), (c) "locked" diester **Pd-6** efficiently catalyzes the oxidation of cholesterol by singlet oxygen, (d) all new compounds show strong absorption above 650 nm, and (e) the presence of functional groups that can be transformed and are independent of the chromophore opens a possibility to tune the hydrophilic/lipophilic properties of the sensitizers, since the chlorinic chromophores proved to withstand acidic or basic conditions, as well as photooxygenation. In addition, the very accessible ketonic precursors **H_2-4** and **Pd-4** are also excellent photosensitizers.

Acknowledgment. We thank P. Wehrung for mass spectra.

Supporting Information Available: Experimental procedures for the preparation of **Ni-4**, **Ni-5**, **Ni-6**, **Pd-4**, **Pd-6**, **H_2-4**, **H_2-6**, **Zn-4**, and **Zn-6**; full experimental details for the photosensitized oxidation of cholesterol. This material is available free of charge via the Internet at http://pubs.acs.org.

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