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Regioselective Oxidation of the Phytyl Chain of Pyrochlorophyll *a*

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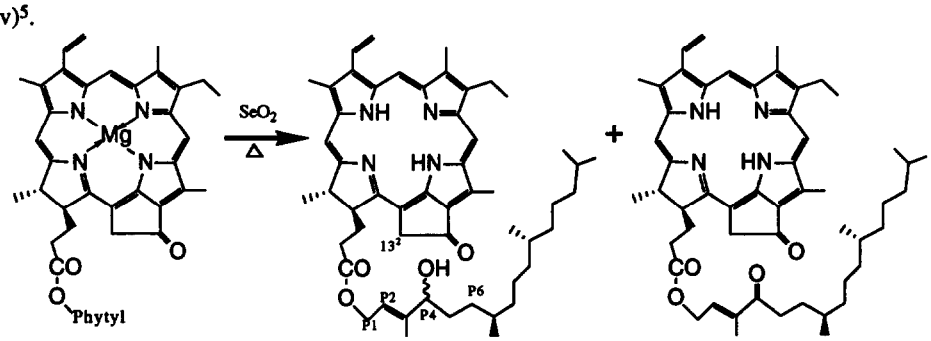
Abstract: *A regioselective oxidation of pyrochlorophyll a is described. Selenium dioxide is introduced for the hydroxylation or carbonylation of the P-4 allylic position in the phytyl chain of the phorbin.*

Despite the extensive studies on oxidation of chlorophyll *a* and its derivatives[1], thus far there have been no reported reactions of synthetic interest concerning the selective oxidation of the phytyl group. Nevertheless, that type of reaction seemed to be of great interest, considering the possibility of using the phytyl chain as a site of binding for different kinds of functionally active substituents. This possibility is very important for creating new tumour photosensitizers of the 'second generation' [2] (using polyalcohols or carbohydrates as substituents) or for constructing new models for investigation of photoinduced electron transfer[3] (using different types of quinones as substituents). We report here an efficient method for the regioselective oxidation of the phytyl chain in pyrochlorophyll *a* using SeO_2 as an oxidant.

Chlorophyll *a* was quantitatively converted into 13²-demethoxycarbonyl-chlorophyll *a* (pyrochlorophyll *a*) (**1**) by heating its degassed pyridine solution at 100 °C in a sealed tube[4]. The pyrochlorophyll *a* obtained was then treated with SeO_2 (1.5 - 4 equivalents) in ethanol, pyridine or 1,4-dioxane solution under argon and with refluxing and magnetic stirring. The reaction was monitored by TLC on cellulose (eluent: *n*-heptane - pyridine, 9:1, v/v)[5].



1 **2** **3**

The choice of solvent was found to be very critical. The oxidative power of SeO_2 is dependent on the temperature or, in other words, on the boiling point of the solvent used[6]. From that point of view, EtOH appeared to be the least useful solvent; only traces of oxidation products were detected even after several days of reflux. In contrast, the reaction time in pyridine and dioxane was only some hours. In dioxane, the P-4(R, S)-hydroxy derivative (**2**) was obtained in a yield of 32% after 5 hours of refluxing, using 4 equivalents of SeO_2. Only small amounts of P-4-oxo-13²-demethoxycarbonyl-pheophytin *a* (**3**) and unreacted pyropheophytin *a* were detected. If the refluxing was continued up to 10 hours, the hydroxy derivative (**2**) was completely converted into the oxo derivative (**3**) with an overall yield of 21%. Compared to dioxane, the reaction in refluxing pyridine appeared to be less selective; both products **2** and **3** were formed in 1 hour, despite the variation of the amount

of SeO_2. Thus, according to our results, 1,4-dioxane is the solvent of choice for the regioselective oxidation of the phytyl group.

It should be noted that the first step of the reaction sequence in 1,4-dioxane and ethanol is pheophytinization which can be attributed to the formation of selenious acid (H_2SeO_3) as an intermediate in the oxidation process[7]. No demetalation was observed in pyridine. Thus, if it is desirable to retain the central magnesium through the oxidation process, pyridine should be chosen as solvent, despite its lower selectivity and lower yield of final products. One would anticipate the oxidation of the 13^2-position of the isocyclic ring to be a significant reaction, but our results show that this is not an important pathway under the conditions used. In addition to the principal products, **2** and **3**, we also observed several polar by-products that moved very slowly on the TLC plate[5]. These were not further studied.

The reaction products were purified on a silica column with CCl_4-acetone (6:1, v/v) as an eluent for metal-free derivatives **2** and **3**. Mg-complexes of **2** and **3** were purified on a sucrose column with *n*-hexane-pyridine (5:1, v/v) as an eluent . All the substances obtained were characterized by ^1H and ^{13}C NMR spectroscopy (the most characteristic resonances are summarized in Table 1) and by FAB mass spectra[10]. The assignments of NMR spectra have been done using 2D-correlated spectroscopy (COSY and HETCOR techniques).

Table 1. Selected Chemical Shifts for Pyrochlorophyll *a* and Its Derivatives[11].

Compound[a]	^1H resonances				^{13}C resonances			
	P-1	P-2	P-4	13^2	P-1	P-2	P-4	13^2
Pyropheophytin *a*	4.56	5.22	1.94	5.19	61.4	117.8	39.7	47.9
(**2**)	4.69	5.58	4.01	5.13	61.4	118.8	76.9	48.2
(**3**)	4.59	6.27	-	5.19	61.3	135.9	201.4	48.1
PyroChl *a* (**1**)[b]	4.38	4.97	1.75	4.33	61.3	119.5	40.5	49.2
Mg-complex of (**2**)	4.59	5.15	3.75	4.79	61.7	119.4	76.9	49.3
Mg-complex of (**3**)	4.55	6.30	-	4.92	62.1	135.5	201.6	49.2

[a]In $CDCl_3$ for Mg-free compounds, in acetone-d_6 for Mg-complexes; [b]Ref. 8 for ^1H NMR, ref. 9 for ^{13}C NMR data

In summary, selenium dioxide is shown to be an efficient and a rather regioselective reagent for the oxidation of the allylic position P-4 of the phytyl chain in pyrochlorophyll *a* . The compounds obtained are unique and have not been previously reported . Studies on the oxidation of other chlorophyll derivatives are now underway in our laboratory and the results along with further spectroscopic studies of the products will be reported elsewhere.

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10. Mass spectral data: **2** ($C_{53}H_{72}N_4O_4$)-*m/z* (FAB) 829 ($M+H^+$), **3** ($C_{53}H_{70}N_4O_4$)-*m/z* (FAB) 827 ($M+H^+$).
11. The complete NMR data will be reported elsewhere.

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