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Oxidative Silylation of Zinc Pyropheophorbide *a* Methyl Ester

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***Abstract*.** Silylation of zinc pyropheophorbide *a* methyl ester with chlorotrimethylsilane in the presence of oxygen resulted unexpectedly in the formation of the novel oxygen-bridged dimer (**2**), the structure of which was assigned using mass spectrometric and NMR methods. Copyright © 1996 Elsevier Science Ltd

Silylation of aldehydes and ketones is known to enhance the susceptibility of the adjacent carbon atom towards electrophilic substitution.[1] Based on this observation, we embarked on the synthesis of silylated enols of chlorophyll *a* derivatives. The readily available pyropheophorbide *a* was chosen as the starting compound. We expected that in this case enolization of the cyclopentanone ring would not proceed as smoothly as in the previously reported silylation[2] of chlorophyll *a* and pheophorbide *a* due to the absence of the 13^2-methoxycarbonyl group.

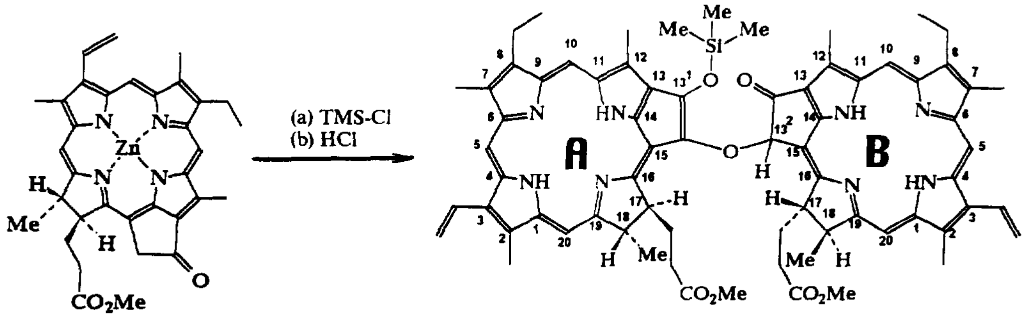
The zinc complex (**1**) of pyropheophorbide *a* methyl ester was treated at room temperature in air with chlorotrimethylsilane and sodium iodide in acetonitrile. A rapid reaction occurred as judged by the colour change. After 40 min. the mixture was evaporated, the residue was dissolved in chloroform and separated by preparative TLC on silica, eluting with chloroform: acetone = 6:1.

After demetallation ($CHCl_3$, HCl), chromatographic separation on silica with chloroform: acetone (20:1) gave the product. No other chemical transformation (such as cleavage of the trimethylsilyl group) occurred during demetallation. Thus remetallation of the product gave the zinc complex from which it had been formed (TLC; electronic absorption spectrum λ_{max}, $CHCl_3$: 411 and 665 nm).

The final purification of the demetallated product was carried out by HPLC (Sepharon C18 column, 10 x 250 mm, $CHCl_3$: MeOH = 3:7 v/v. Yield 55% based on **1**). The electronic absorption spectrum showed λ_{max}, $CHCl_3$: 402.5 and 677 nm. However preliminary examination of the physical and chemical properties of the product showed that they did not correspond to those of the expected trimethylsilyl ether of the enol of pyropheophorbide *a* methyl ester. Thus the ^1H NMR spectrum had six signals in the *meso*-region, and two sets of signals from protons of the vinyl group, and from some of the other substituents. Nevertheless the spectrum had a characteristic sharp peak at δ 0.30 which we assigned to the trimethylsilyl group. This spectrum could be explained in terms of either the formation of two isomers (eg the trimethylsilyl group could be located at N-21 or N-23) or the formation of a dimeric pyropheophorbide structure. The observation of a singlet peak for the trimethylsilyl group, and some other peaks, did not accord with the first explanation. To test the dimer hypothesis, the product was examined by gel chromatography on Fractogel TSK HW-40(s) (Merck) under conditions which separate dimeric and oligomeric fractions of haematoporphyrin derivative.[3] Pyropheophorbide *a* methyl ester was used as the standard: the new compound showed a retention time consistent with a dimeric structure.

Further evidence for the dimeric structure was obtained from mass spectra, which were measured under various conditions. When the sample was ionised with ^{252}Cf decay products, two peaks with *m/z* 1185.2 and 1096.1 were observed in the high mass region (time-of-flight mode).[4] The first of these peaks was assigned to the molecular ion; the second signal to the loss of the trimethylsilyloxy group $[(M + H) - OSiMe_3]^+$. The mass spectrum also contained fragments with *m/z* 636.2 and 548.2.

The chemical composition of the latter peaks was deduced from high resolution FAB spectra:[5] accurate mass measurement of the first peak gave 635.3075. $C_{37}H_{43}N_4O_4Si$ requires 635.305 and corresponds to a trimethylsilylated pyropheophorbide *a* methyl ester containing an extra oxygen atom. The second cleavage peak, at *m/z* 547.2, corresponds to pyropheophorbide *a* methyl ester. These two fragments arise due to cleavage of the molecular ion of the dimer, which in this mass spectrometry mode appeared at *m/z* 1184. The FAB mass spectrum also contained an ion with *m/z* 1206, corresponding to $M + Na^+$



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On the basis of these results, structure (2) was proposed for the dimer. The results of high resolution ^1H NMR spectroscopy are consistent with this proposal.

NMR spectra of (2) were recorded with a Bruker AMX-600 spectrometer. COSY and NOESY spectra[7,8] were recorded in a phase-sensitive absorption mode using TPPI in t_1.[9] The NOESY spectrum[7] was recorded with a mixing time of 0.5 s. Two-dimensional spectra were collected as a 410-512 (t_1) real and 1024 (t_2) complex point time domain matrix with a spectral width of 8500 Hz in both dimensions.

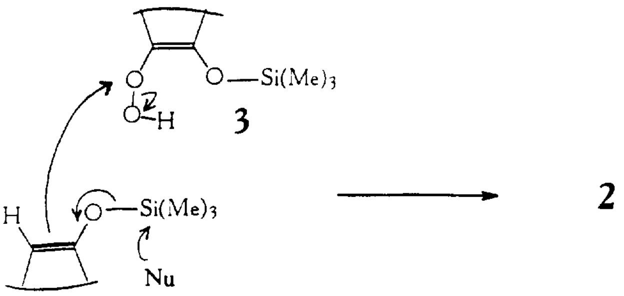
The one-dimensional ^1H NMR spectrum at this field showed a doubling of the characteristic resonances of the pheophorbide *a* system. Unambiguous assignment of all the proton resonances in (2) was achieved with the help of two-dimensional spectra. The COSY spectrum was used to identify spin systems and the NOESY spectrum was used to obtain spatial relationships in the usual way. The final assignments were made on the basis of NOE correlations which reveal spatial proximity between proton pairs.

The resonance of the 13^1(A) - $OSiMe_3$ group was used at the starting point. This resonance has a strong NOE cross peak with a methyl singlet at δ 0.77, which was assigned to the 12(A)-CH_3 function. This in turn gives a strong cross peak the with *meso* proton signal (one of six present) at δ 9.00. This resonance was therefore assigned to 10(A)-H. The 10(A)-H resonance also correlates with 8(A)-Et, indicating spatial proximity between these two groups. Following this procedure, all the proton resonances in macrocycle A were assigned. The same approach was used to assign the resonances in macrocycle B. In contrast to A, B does not have a $OSiMe_3$ group, but the spectrum has an extra signal at δ 6.70 due to 13^2-H. It gives strong NOE cross peaks with resonances of the 17(B)-propionic residue, and 17(B)-H but relatively weak ones with 18(B)-CH_3 and 18(B)-H. Assignment of NH resonances was made on the basis of strong NOE cross peaks between NH pairs, and weak NOE cross peaks with *meso*-positions. The assignments of all protons of (2) is shown in Table 1.

Table 1. ^{1}H NMR Spectral Data for Dimer (**2**) (d_6-DMSO, 600 MHz).

Proton	Macrocycle A	Macrocycle B
5-*meso*	9.73 (s)	9.50 (s)
10-*meso*	9.00 (s)	9.42 (s)
20-*meso*	9.30 (s)	9.11 (s)
3^1-C$\underline{H}$=CH$_2$	8.26 (dd)	8.23 (dd)
3^2-CH=C$\underline{H}_2$	6.31 (dd), 6.12 (dd)	6.42 (dd), 6.23 (dd)
8^1-C$\underline{H}_2$-CH$_3$	3.33 (q)	3.54 (q)
8^2-CH$_2$-C$\underline{H}_3$	1.23 (t)	1.48 (t)
2-CH$_3$	3.50 (s)	3.53 (s)
7-CH$_3$	3.09 (s)	3.19 (s)
12-CH$_3$	0.77 (s)	2.55 (s)
18-CH$_3$	1.99 (d)	2.28 (d)
17-H	5.23 (m)	5.67 (m)
18-H	4.82 (q)	4.69 (q)
17^1-CH$_2$	2.99 (m), 2.31 (m)	2.88 (m), 2.55 (m)
17^2-CH$_2$	2.77 (m), 2.23 (m)	2.60 (m)
13^3-COOCH$_3$	3.57 (s)	3.42 (s), 2.32 (m)
13^1-OH(13^2-H)	—	6.70 (s)
13^1-SiMe$_3$	-0.30 (s)	—
NH	-0.31 (s) and -2.34 (s)	-0.01 (s) and -1.75 (s)

We conclude that silylation of zinc pyropheophorbide *a* methyl ester in the presence of air results in the formation in reasonable yield of the dimer (**2**) with an ether bridge. The reaction is novel and surprising: ahead of work to define the mechanism more closely, we rationalise it as shown in the scheme. The silylated enol hydroperoxide (**3**), is thought to be a key intermediate, which could be formed by alternative routes. Zinc chlorins are known to be easily autoxidised.[10] Reaction of (**3**) with another molecule of the silylated enol in the presence of a suitable nucleophile then generates dimer (**2**).



It is unclear why the second trimethylsilyl group remains. Possibly the carbonyl group on the neighbouring macrocycle to some extent stabilises this group, since, as the ^{1}H NMR data show, the trimethylsilyl group is located close to the substituents of the cyclopentanone ring of macrocycle B (NOESY interaction $Me_3Si \rightarrow$ H-10).

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4. Mass spectra were measured on a MSBKh instrument (SELMI, Sumy, Ukraine). Ionization was caused by ^{252}Cf fission products, and a time-of-flight monitoring ion analyzer was employed.

5. FAB mass spectra: VG Autospec at Swansea using caesium ion bombardment (25 kv) on sample in *p*-nitrobenzyl alcohol.

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