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Transesterification of the α-Keto Ester in Methyl Pheophorbide-*a*

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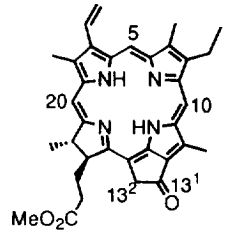
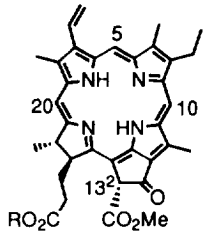
Abstract: *Transesterification of the α-keto methyl ester in methyl pheophorbide-a proceeds smoothly under neutral conditions, allowing the preparation of a variety of models such as steroid-pheophorbide, pyromellitimide-pheophorbide, thymidine-pheophorbide, pheophorbide dimer, and porphyrin-pheophorbide.* Copyright © 1996 Elsevier Science Ltd

Chlorophyll is the most abundant and important pigment in plants and plays the central roles in photosynthesis. During the past two decades, porphyrin-based models have been demonstrated to be useful for studies on electron and energy transfer reactions.[1] Several groups used a pyropheophorbide unit as a better model for chlorophylls and related pigments.[2] However, the unique structures of chlorophylls and related pigments have limited synthetic methods applicable for the attachment of an electron donor and an electron acceptor to these pigments. Therefore, efficient synthetic methods allowing a facile attachment of a variety of functional groups to these photosynthetic pigments are highly desirable. In this communication, we report a facile transesterification of the α-keto ester of methyl pheophorbide-*a*, which provides a convenient access to new pheophorbide-based models.



Methyl pyropheophorbide-*a*

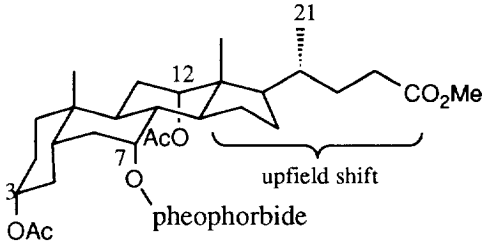


1 R = Me
2 R = Et

First, we describe the transesterification of methyl pheophorbide-*a* (**1**) with methyl 3α,12α-diacetoxy-7α-hydroxy-5β-cholanate (**3**).[3] A 1:1 mixture of **1** and **3** was refluxed in toluene for 3 h under N_2 in the presence of 2 equiv of 2-chloro-1-methylpyridinium iodide (CMPI) and 4 equiv of 4-(*N*,*N*-dimethylamino)pyridine (DMAP). Chromatographic separation over a silica gel column followed by

recrystallization from CH_2Cl_2/hexane gave **4a** in 63% yield. Its FAB-Mass spectrum shows the parent mass peak (1080.6) and an intense peak (547.4) derived from the fragmentation at the α-keto position (**4** - CO_2R). The 500 MHz ^1H NMR spectrum shows that the 13^2-H signal appears at 6.17 ppm and the corresponding methyl ester peak is replaced by a full set of the steroid signals. When ethyl pheophorbide-*a* (**2**)[4] is used instead of **1** to determine which ester is exchanged, the ethyl peak remains and the methyl peak disappears, supporting the transesterification at the 13^2 ester. Interestingly, the chemical shifts of a part of the steroid moiety are upfield shifted. Detailed examination using the 2D-COSY experiments indicates that upfield shifts are observed mainly for the C- and D-ring protons by 1-2 ppm.[5] Table 1 shows the chemical shifts of several characteristic protons of the steroid moiety. The observed high field shifts that are due to the ring current of the pheophorbide macrocycle indicate that the cholic acid part locates just over the macrocycle.

Table 1. ^1H NMR Chemical Shift Changes of Steroid by Ring Current Effect of Pheophorbide-*a*

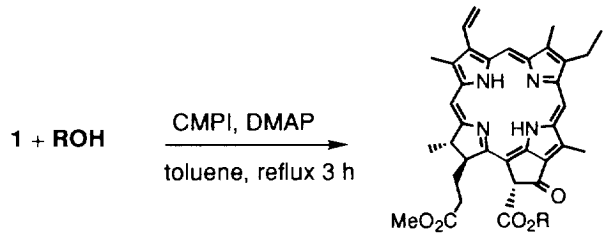


compd.	3-H	12-H	21-H	CO_2Me
3(δ, ppm)	4.56	5.09	0.83	3.66
4a(δ, ppm)	4.67	4.22	-0.33	3.49
Δδ (ppm)	+0.11	-0.87	-1.16	-0.17

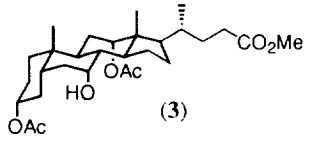
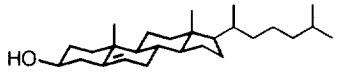
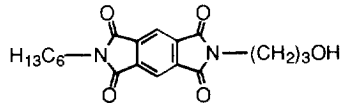
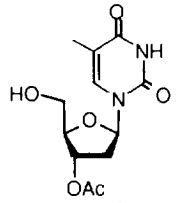
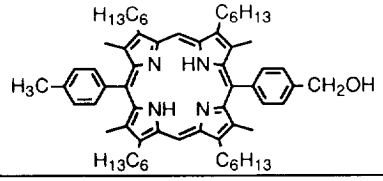
Various alcohols were subjected to this transesterification and the results are summarized in Table 2. Primary and secondary alcohols gave good results under these conditions. Particularly, sterols gave good results (entries 1 and 2). The reaction with ethylene glycol gave pheophorbide dimer **4e** (entry 5), which displays no particular electronic interactions between the two macrocycles. Tertiary alcohols such as *t*-butyl alcohol and 4-phenyl-bicyclo[2.2.2]octane-1-ol[6], and phenol were found to be unreactive in this transesterification. The utility of this reaction has been further demonstrated by one-step synthesis of electron acceptor (pyromellitimide)-linked pheophorbide **4f** (entry 6) and nucleic acid (thymidine)-linked pheophorbide **4g** (entry 7). The former molecule may be photoactive and the latter one may be useful as an adenine recognizing receptor. Finally, pheophorbide-porphyrin dyad **4h** was prepared essentially by the same way with a hydroxy-substituted porphyrin (entry 8). The absorption spectrum of **4h** in THF is the simple sum of those of the respective subunits, while the steady-state fluorescence spectrum exhibits only the emission from the pheophorbide moiety, indicating a quantitative singlet-singlet energy transfer from the porphyrin to the pheophorbide. Detailed photochemistry of **4h** will be reported elsewhere.

The mechanism of the reaction is not clear at the present stage. The reaction proceeds chemoselectively only at the 13^2 ester. The transesterification does not proceed without CMPI, while DMAP can be replaced by other bases such as triethylamine without a significant reduction in the product yield. This reaction requires high temperature and does not proceed in refluxing CH_2Cl_2 or CH_2Cl_2-toluene 1:1 mixture. Epimeric isomers at the 13^2 position of pheophorbide are sometimes contaminated in the reaction mixtures but in most cases the amounts of such epimers are small and the desired products are readily purified by the chromatographic method.

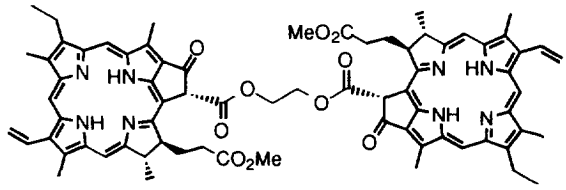
Table 2. Transesterification of the α-Keto Ester of Methyl Pheophorbide-*a* (**1**)



4

Entry	ROH	Product	Yield[a]/%
1	 (**3**)	**4a**	63
2		**4b**	57
3	C_2H_5OH	**4c**	41
4	$C_{18}H_{37}OH$	**4d**	38
5	$HO(CH_2)_2OH$	**4e**[b]	14
6		**4f**	33
7[c]		**4g**	41
8		**4h**	46

[a]Isolated yields based on the amounts of **1** used. [b]Pheophorbide dimer. [c]See ref. 7.



4e

This reaction is useful in attaching a variety of donors and acceptors to the pheophorbide pigment. We are now trying extension of the present transesterification, to further elaborated photosynthetic models.

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3 Mathivanan, P.; Maitra, U. *J. Org. Chem.* **1995**, *60*, 364-369.
4. Ethyl pheophorbide-*a* is obtained by stirring a solution of methyl pheophorbide-*a* in ethanol in the presence of conc. H_2SO_4.
5. The methylene protons in the D-ring appear in -1.6, -1.3, and -0.3 ppm.
6. Gray, G. W.; Kelly, S. M. *J. Chem. Soc. Perkin Trans. II* **1981**, 26-31.
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