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β-Keto ester aminolysis of pheophorbide *a* methyl ester: a facile route for asymmetric chlorin ring substitution

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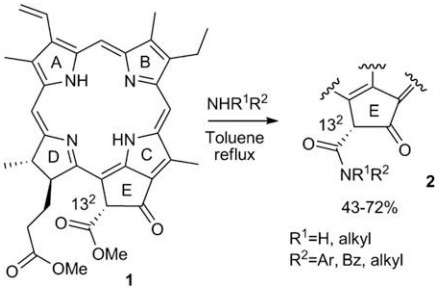
ABSTRACT

A chemoselective aminolysis of the β-keto ester of pheophorbide *a* methyl ester is demonstrated opening a facile access to an asymmetric amide functionalization of a chlorin ring using a range of aromatic and aliphatic, primary and secondary amine nucleophiles. Aminolysis of pheophorbide *a* methyl ester with *trans*-1,2-diaminocyclohexane is shown to give a symmetric open face chlorin dimer.

There are only a limited number of synthetic reactions that can be applied to chlorophylls (Chl) or pheophorbides (Pheo, Chls, Mg and phytyl-free derivatives) with decent chemoselectivity and good yields.[1] The methoxycarbonyl group at the 13^2 position (Scheme 1) makes these compounds susceptible to oxidative allomerization and ring cleavage reactions under reasonably mild chemical conditions. This group tolerates non-oxidative acidic conditions to some extent, but fairly weakly basic and nucleophilic conditions, for example, ammonia, have been reported to induce ring E cleavage aminolysis of these pigments.[2] In an exception to this, Osuka and co-workers previously introduced a chemoselective 2-chloro-1-methylpyridinium iodide assisted and base-catalyzed transesterification reaction for the β-keto ester of pheophorbide *a* methyl ester.[3] Encouraged by this, we decided to study whether an analogous strategy could be applied with Pheo *a* methyl ester and amines to achieve chemoselective β-keto ester aminolysis. It is also known that aminolysis of β-keto esters is usually a facile reaction compared with an unactivated ester.[4] In this work we present reaction conditions for, and the scope of the chemoselective aminolysis of Pheo *a* methyl ester.[5]

We began our aminolysis study simply by refluxing Pheo *a* methyl ester and a slight excess of amine in dry toluene (Scheme 1). To our surprise, we obtained moderate to good yields (43–72%) of amides **2** with various mono amines including aliphatic, aromatic, primary and secondary (Table 1).[6] Very satisfactorily in most cases the aminolysis product was formed as a stereochemically enriched 13^2 *R*-isomer (>90%).[7] This ratio likely originates from the starting material. Undoubtedly, the *R*-isomer is also the thermodynamically more stable stereoisomer. However, a mixture of isomers could be expected to form by keto-enol equilibrium. Especially for the small alkyl amides, a larger distribution of the stereoisomers would be probable if this, for example, base-catalyzed, equilibrium existed in the reaction media.[8] The only side product was the 13^2-demethoxycarbonyl 'pyro' product, (3^1,3^2-didehydrophytochlorin), which is known to be formed when a Pheo *a* methyl ester is heated in the presence of base and varying amounts of water.[9]

Disappointingly, further reaction optimization did not give any improvement. The use of base additives such as triethylamine, DMAP or pyridine did not affect the yields. Instead, the use of a large excess of amine yielded classic ring cleavage products **3** (80% yield). This type of product was first synthesized by Fischer and was classified as an amine adduct.[2a] This reaction takes place at 40 °C. The same ring cleavage reaction occurs for the 13^2 amide of Pheo *a* when it is stirred with mild heating with excess of amine, producing compound **4** (59% yield). We presume that the ring cleavage reaction could proceed via a hemiaminal intermediate as depicted in Scheme 2. In the proposed mechanism, ring cleavage is induced by the basic environment which is created by the excess of amine. It has been suggested that in the general mechanism of β-keto ester aminolysis, the reaction could take place via a hemiaminal intermediate rather than being promoted by enolization or



Scheme 1. Chemoselective β-keto ester aminolysis of Pheo *a* methyl ester.

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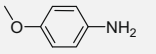
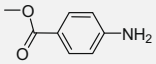
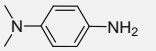
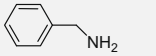
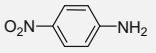
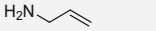
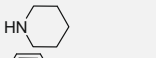
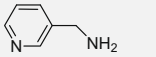
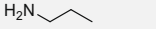
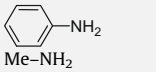
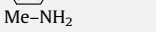
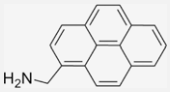
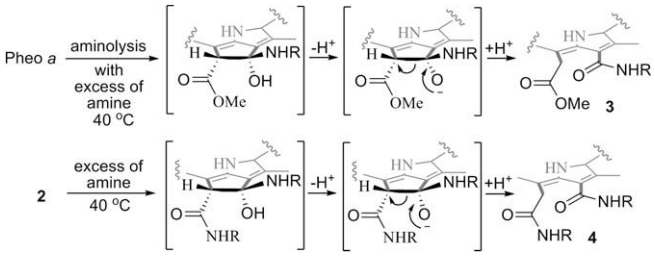
Table 1
Aminolysis of Pheo *a* methyl ester with various amines

Entry	Amine	Yield[a] **2** (%)
1		72
2		61
3		59
4		59
5		55
6		55
7		54
8		49
9		46
10		43
11		43
12		43

[a] Yield after flash column chromatographic purification.



Scheme 2. Suggested ring E opening mechanism for Pheo *a* methyl ester and the corresponding 13^2 amide with an excess of amine.

inductive effects.[4] The observed high diastereomeric excess of the *R*-isomer (at $C13^2$) makes a reaction pathway via an enol intermediate unlikely, because epimerization of $C13^2$ would also take place via an enol intermediate.[10] Additionally, the proposed ring cleavage pathway via the hemiaminal suggests that a similar intermediate could be relevant in the aminolysis. We are currently studying the reaction kinetics and performing theoretical computations to shed light on this enigma.

In order to elucidate further the scope of this reaction, we performed the aminolysis of pheo *a* methyl ester with *trans*-1,2-diaminocyclohexane to show the facility of the reaction in the synthesis of chlorin dimers. The reaction proceeded as smoothly as in the case of mono amino alkanes (Table 1). As a result, we obtained a symmetric chlorin dimer, compound **5** (Scheme 3), whose NMR spectrum showed only one set of chlorin signals. A closer inspection of the ^{1}H NMR spectral changes between the monomer and dimer revealed that the 12^1 (–CH_3), 13^2 (–CH–) and 17 (–CH–) protons were considerably deshielded, whereas the 17^5 (–CH_3) ester protons were shielded in $CDCl_3$ (Fig. 1). It can be assumed that both of these shielding effects are induced by ring currents of the neighbouring chlorin ring;[11] hence the values give information about the mutual positions of the rings. The observed deshieldings likely arise when the protons are located on an edge position with respect to the neighbouring chlorin ring, while the shielding at 17^5 (–CH_3) is induced from the top position. Overall, this fits with an open dimer conformation, in which the chlorin planes are not overlapping, but the edges of the rings are in close contact.

^{1}H NMR measurements at variable temperatures showed that the amide proton resonance was the only temperature sensitive signal. Deshielding of the amide proton was observed by lowering the temperature, which implies the presence of hydrogen bonds. Hydrogen bonding character could be further confirmed by the 3347 cm^{-1} IR N–H stretching, which is typical for a hydrogen bonded amide (3300–3350 cm^{-1}).[12]

Molecular modelling of compound **5** using the DFT B3LYP method at the 3-21G* level resulted in a C_2-symmetric open conformation dimer as an energy optimized structure (Fig. 2), which is in good agreement with NMR data: deshielded protons are located on the edge of the adjacent chlorin ring, the shielded 17^5 (–CH_3) is on the top and the amide protons are at hydrogen bonding distance (1.90 Å).

We have recently demonstrated that with a suitable bisamide linker at the 17^5 position, the tethered chlorin dimer folds in non polar solution into a closed conformation.[13] Herein, compound **5** exemplifies that a dimer equipped with a rigid amide linker at the 13^3 positions adopts an open conformation(s). Its photophysical properties will be studied in our future work.

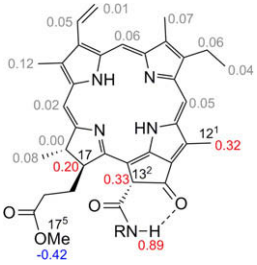
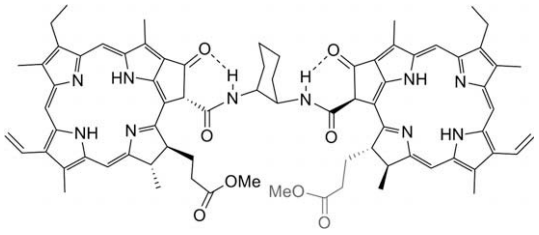


Figure 1. $\Delta\delta$ aggregation map of *trans*-1,2-diaminocyclohexane linked dimer $\Delta\delta_5$ = [compound **5**] – [(entry 9)] in $CDCl_3$.



Scheme 3. Structure of compound **5**, *trans*-1,2-diaminocyclohexane linked chlorin dimer.

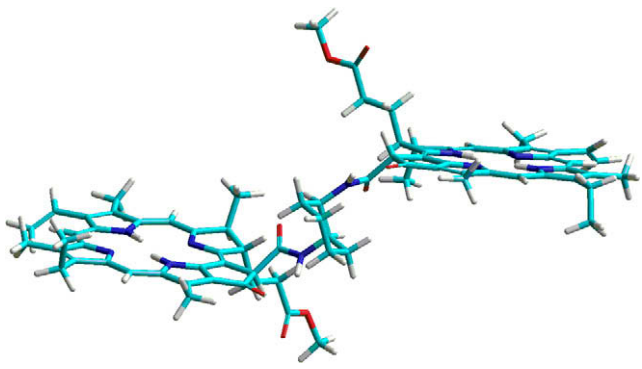


Figure 2. B3LYP 3-21G* geometry optimized C_2-symmetric open conformation dimer (compound **5**).

In summary, we have studied the scope of β-keto ester aminolysis of Pheo *a* methyl ester. The method offers facile access to asymmetric substitution of a chlorin ring. This paves the way to novel asymmetrically linked and geometrically well-defined chlorins, which are molecules of photophysical interest, for example, for electron donor-acceptors or exciton transfer studies.

Acknowledgements

Dr. Petri Heinonen is acknowledged for HRMS spectra. We thank the Academy of Finland (nos. 113317 and 134820) and Foundation for Research of Natural Resources in Finland for financial support of this research.

Supplementary data

Full experimental compound characterization, ^{1}H and ^{13}C NMR spectra are presented for all the compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.121.

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4. Labelle, M.; Gravel, D. *J. Chem. Soc., Chem. Commun.* **1985**, 105–106.
5. In parallel with our studies Buravlev et al. have shown that the aminolysis of Pheo *a* can be carried out with a benzylic phenol amine under similar conditions: (a) Buravlev, E. V.; Chukicheva, I. Y.; Belykh, D. V.; Kuchin, A. V. *Chem. Nat. Comp.* **2007**, *43*, 678–681; (b) Buravlev, E. V.; Chukicheva, I. Yu.; Belykh, D. V.; Kuchin, A. V. *Chem. Nat. Comp.* **2008**, *44*, 598–602.
6. *General procedure:* benzylamine (entry 4) (6.4 mg, 0.06 mmol) was added to a dry toluene solution (10 mL) (distilled over Na) of pheophorbide *a* (30.0 mg, 0.05 mmol), and the mixture was refluxed under argon at 130 °C. The reaction was monitored by TLC (eluent 1:1 hexane/ethyl acetate). Reflux was continued for 4 h (e.g., for *p*-nitroaniline, entry 5, the reaction time was 16 h). The reaction mixture was washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel chromatography (5:1 to 1:1, hexane/ethyl acetate, gradient) to give the product.
7. As analyzed by integrals of ^{1}H NMR signals and characterized with NOESY experiments.
8. *For example, in the case of propylamine (entry 9)*: aminolysis yielded the *R* enantiomer at $C13^{2}$ with 96% de, while after the sample had stood for a few days in the presence of a catalytic amount of base, a 90% de of this enantiomer was quantified (thermodynamic equilibrium).
9. Amounts of added water facilitates the demethoxycarbonylation when porphyrin compounds were heated in pyridine (or its derivatives); U.S. Patent 5973,141; CA 2351372.
10. (a) Katz, J. J.; Norman, G. D.; Svec, W. A.; Strain, H. H. *J. Am Chem. Soc.* **1968**, *90*, 6841–6845; (b) Hynninen, P. H.; Lötjönen, S. *Magn. Reson. Chem.* **1985**, *23*, 605–615.
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12. The secondary N–H bond stretched at this region in the IR spectra in entries 1–5 and 8–12 which indicates hydrogen bonding. Characteristic IR N–H bond region: Gellman, S. H.; Dado, G. P.; Liang, G.-B.; Adam, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164–1173.
13. Nikkonen, T.; Haavikko, R.; Helaja, J. *Org. Biomol. Chem.* **2009**, *7*, 2046–2052.