Synlett A. Briš et al. Letter

Synthesis of Chlorins by Diels–Alder Cycloadditions of Pheophorbide a and Its Derivatives

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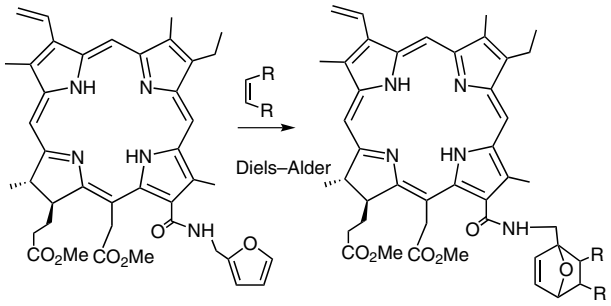
Dedicated to Professor Ron Warrener on the occasion of his 80th birthday



Received: 05.12.2014
Accepted after revision: 21.01.2015
Published online: 18.02.2015
DOI: 10.1055/s-0034-1380176; Art ID: st-2014-d1002-l

Abstract The Diels–Alder reaction was exploited for the preparation of novel long-wavelength chlorin photodynamic therapy photosensitizers. The styryl group and furan carboxamide substituents were used as diene components in [4+2] cycloaddition functionalizations.

Key words cycloaddition, Diels–Alder reaction, photodynamic therapy, porphyrins

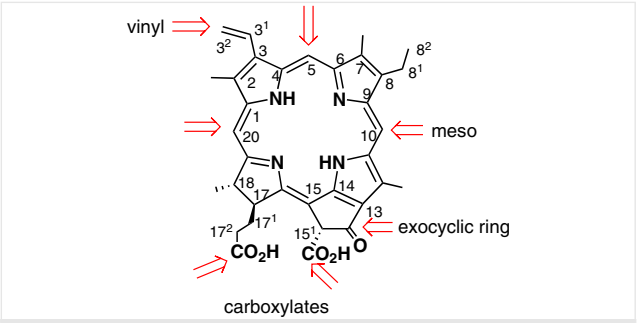


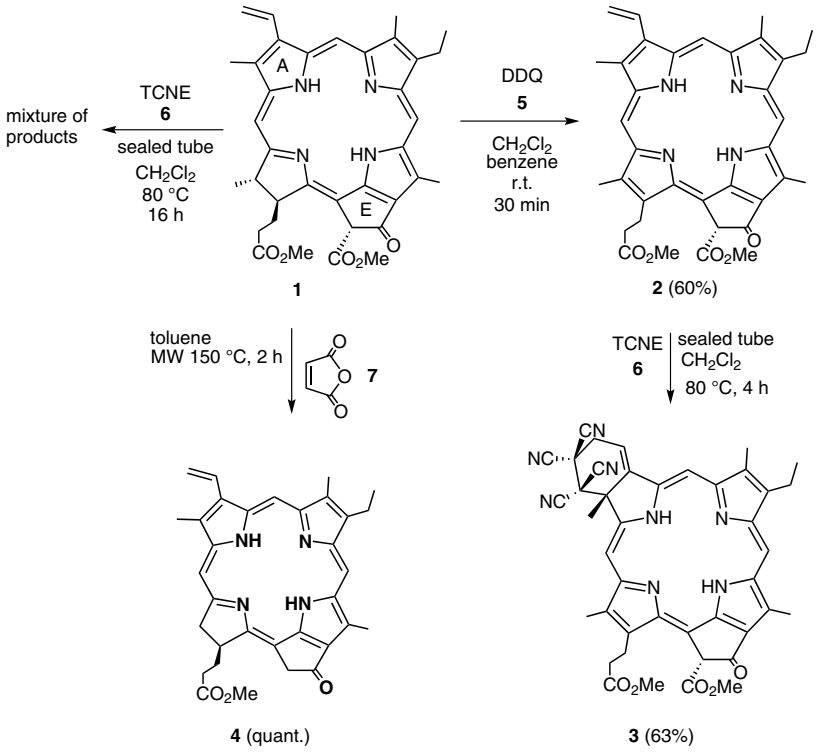
Figure 1 Functionalization points of pheophorbide a

Chlorins, which are porphyrin derivatives, are widely used as sensitizers in photodynamic therapy (PDT).[1,2] A number of chlorin derivatives were prepared by functional transformations of pheophorbide a and its various derivatives in the search for efficient PDT photosensitizers. Several points around the porphyrin core were identified for functionalization (Figure 1). One of the synthetic approaches to functionalized chlorins exploits Diels–Alder cycloadditions;[3] here, the chlorin acts as a diene component (consisting of π-bonds of vinyl substituent and ring A pyrrole). In a continuation of our synthetic endeavors in cycloaddition[4] and porphyrin chemistry,[5] the application of porphyrins in PDT,[6] and with the aim of preparing novel long-wavelength PDT sensitizers, we studied selected Diels–Alder transformations of pheophorphyrin a and pheophorbide a. These results are the topic of this paper.

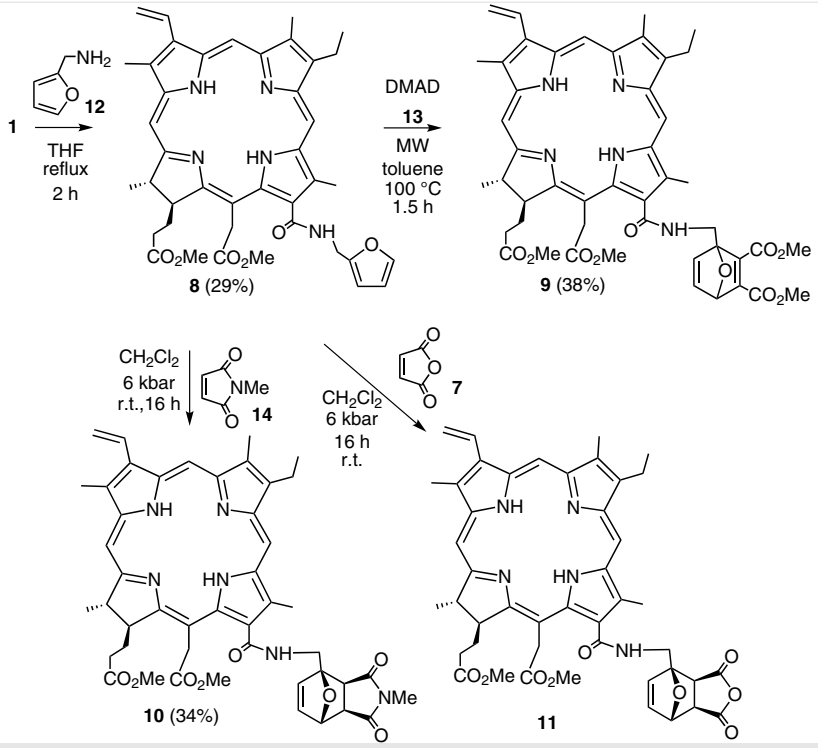
Dimethyl pheophorbide a (**1**) was isolated from *Spirulina Pacifica*. Dimethyl pheophorphyrin a (**2**) was obtained by oxidation of **1** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; **5**) in 60% yield by following the procedure described for chlorin e_6.[7] Whereas the vinylic group of **2** can participate in Diels–Alder reactions, it seems to react optimally only with very reactive/electron-poor dienophiles. Hence, heating a mixture of pheophorphyrin **2** with tetracyanoethylene (TCNE; **6**) in dichloromethane solution (sealed tube, 4 h, 80 °C) produced, after chromatographic purification, Diels–Alder adduct **3** across the 2–3^2 positions in 63% yield (Scheme 1) as a 1:1 mixture of 2-epimers.[8] The ^{1}H NMR spectrum confirmed the presence of the new exocyclic π-bond in the adduct (a triplet at δ = 7.01 ppm and new methylene multiplet at δ = 4.09 ppm), in conjunction with loss of the vinylic protons, showing that the expected Diels–Alder cycloaddition onto the vinylic double bond had taken place. Another indication that reaction involves ring A is the shift of the C2 methyl signal towards higher field, from δ = 3.38 to 2.36 (2.39) ppm.

Analogous TCNE reaction with **1** (sealed tube, CH_2Cl_2, 16 h, 80 °C) produced a complex mixture of products in which the proton signals of the vinylic and isocyclic E ring moieties, as well as of the 5-*meso* position of **1** were absent in the ^{1}H NMR spectrum.

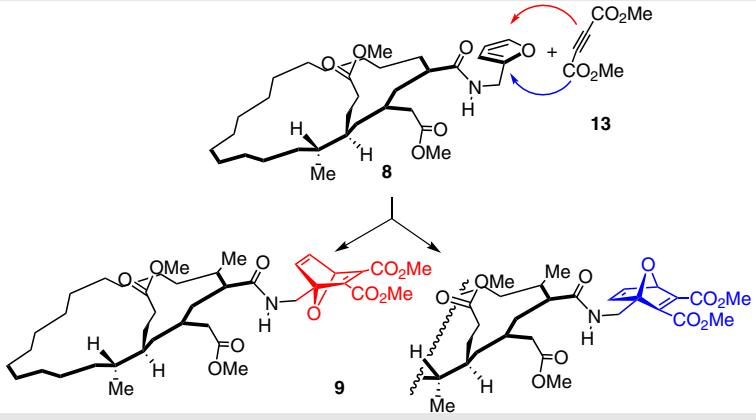
Furthermore, cycloadditions of **1** with maleic anhydride **7** employing various reaction conditions failed both in a sealed tube (chloroform or toluene, 4 d, 120 °C) and under ultra-high pressure (CH_2Cl_2, 6 kbar, 4 d, 70 °C); whereas heating in a microwave reactor at 150 °C produced methyl pyropheophorbide **4** in quantitative yield within two hours.



Scheme 1 Diels–Alder reactions of dimethyl pheophorphyrin a



Scheme 2 Diels–Alder cycloadditions to furyl pheophorbide a



Scheme 3 Formation of 7-oxanorbornadiene analogues

Diels–Alder reactions of **1** with *N*-methyl maleimide **14** (sealed tube, toluene, 14 h, 120 °C), or DMAD (sealed tube, toluene, 3 d, 120 °C), gave unchanged starting material. The application of arynes as highly reactive dienophiles was also unfruitful, because **1** was not stable to the reaction conditions. Generation of benzyne from anthranilic acid and isoamyl nitrite in situ by heating in dioxane,[9] or preparation of 4,5-di(trimethylsilyl)benzyne from 1,2,4,5-tetra-(trimethylsilyl)benzene at room temperature (PIDA, TFA, TBAF, DIPEA)[10] afforded intractable mixtures. These results are in good accord with previous reports on the low cycloaddition reactivity of **1**.[6]

An increase in cycloaddition reactivity of **1** was achieved by derivatization of ring E. Nucleophilic ring opening with furfurylamine **12** (THF, reflux, 2 h) afforded chlorin e_6 furfuryl carboxamide **8** in 29% yield (Scheme 2). The furyl moiety showed much higher reactivity towards dienophiles such as dimethyl acetylenedicarboxylate (DMAD; **13**) and *N*-methyl maleimide (MI; **14**).

Thermal Diels–Alder reactions of **8** with DMAD were carried out by conventional heating in a sealed tube or in a microwave reactor. The best yield was achieved under microwave reaction conditions (toluene, 1.5 h, 100 °C, 100 W, 38%), whereas MW heating for one hour gave a somewhat lower conversion of **8** (>90%), and MW heating without solvent produced a complex mixture of products. In contrast, conventional heating of **8** and DMAD in a sealed glass tube (toluene, 100 °C, 16 h), provided 7-oxanorbornadiene derivative **9** cleanly in 38% yield. Introduction of the 7-oxanorbornadiene structure is of particular interest for the possibility of increased tissue selectivity for peptides and proteins containing free thiol groups.[11] Structural determination of product **9** was carried out by combined 1D and 2D COSY and NOESY correlations as well as by comparison with NMR data for model furan and *N*-Boc-furfurylamine cycloadducts with DMAD and MI.[12] NMR analysis revealed the formation of a 13^4 1:1 mixture of diastereoisomers **9**, with duplication of signals, for instance for the methyl esters of 7-oxanorbornadiene moiety, as well as for the 15^2 methyl esters and oxa bridgehead protons. These data are consistent with formation of a new oxanorbornadiene ring system in **9**. The regiochemistry of the oxygen bridge is dependent on the facial orientation between the alkyne and the furan ring of **8** (Scheme 3).

Thermal reversibility of furan DA adducts was precluded by carrying out reaction of **8** with maleimide under ultra-high pressure at room temperature (6 kbar, 14 h, CH_2Cl_2).[13] Chromatographic workup afforded the corresponding 13^4 1:1 epimeric mixture of *exo*-adducts **10** in 34% yield. Analogously, ultra-high pressure cycloaddition of **5** with maleic anhydride (6 kbar, 3 d, r.t., CH_2Cl_2) produced a 13^4 1:1 diastereomeric mixture of *exo*-adducts **11**, as shown by NMR analysis of the crude reaction mixture.

Introduction of bulky substituents at the 13^2 position in products **9** and **7** are predicted to prevent their self-aggregation on steric grounds.[14]

In conclusion, we have shown that pheophorbide a can be effectively functionalized by cycloaddition reactions under conventional and non-classical reaction conditions (MW irradiation and ultra-high pressure).

Acknowledgment

This work was financially supported by the Ministry of Science, Education and Sport of the Republic of Croatia (project No. 098-0982933-3218) and by the Croatian–Chinese Scientific and Technological Cooperation.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380176.

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(8) All novel compounds gave satisfactory ^{1}H, ^{13}C NMR, and high-resolution mass spectra.
Representative ^{1}H NMR spectroscopic data:
Compound 3: Obtained as a 1:1 mixture of 2-epimers. ^{1}H NMR (300 MHz, $CDCl_3$): δ = –1.81, –1.76 (s, 1 H, NH), –0.98, –0.92 (s, 1 H, NH), 1.78 (t, *J* = 7.5 Hz, 3 H, 8^{2}-CH_3), 2.36, 2.39 (s, 3 H, 18^{1}-CH_3), 2.93–3.01 (m, 1 H, 17-CH_2), 3.04–3.11 (m, 1 H, 17^{2}-CH_2), 3.41 (s, 3 H, 7-CH_3), 3.46, 3.47 (s, 3 H, 2-CH_3), 3.70. 3.71 (s, 3 H, 12-CH_3), 3.74, 3.75 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.91 (q, *J* = 7.5 Hz, 2 H, 8^{1}-CH_2), 3.96 (dd, *J* = 13.9, 5.1 Hz, 1 H, 17^{1}-CH_2), 4.05 (dd, *J* = 9.5, 3.1 Hz, 1 H, 17^{1}-CH_2), 4.09 (t, *J* = 4.1 Hz, 2 H, 3^{2}- =CCH_2), 4.11–4.15 (m, 1 H, 17^{1}-CH_2), 6.77, 6.79 (s, 1 H, 15^{1}-CH), 7.01 (t, *J* = 4.1 Hz, 1 H, 3^{1}- =CH), 7.09 (t, *J* = 4.1 Hz, 1 H, 3^{1}- =CH), 9.12, 9.14 (s, 1 H, 20-CH), 9.21, 9.24 (s, 1 H, 5-CH), 9.78 (s, 1 H, 10-CH).
Compound 5: ^{1}H NMR (300 MHz, $CDCl_3$): δ = –1.79 (s, 1 H, NH), –1.59 (br. s, 1 H, NH), 1.69 (t, *J* = 6.6 Hz, 3 H, 8^{2}-CH_3), 1.71 (d, *J* = 7.3 Hz, 3 H, 18^{1}-CH_3), 1.76–1.84 (m, 1 H, 17-CH_2), 2.11–2.17 (m, 1 H, 17-CH_2), 2.18–2.25 (m, 1 H, 17-CH_2), 2.46–2.55 (m, 1 H, 17-CH_2), 3.31 (s, 3 H, 7-CH_3), 3.48 (s, 3 H, 12-CH_3), 3.53 (s, 3 H, 2-CH_3), 3.59 (s, 3 H, 15-OCH_3), 3.73 (s, 3 H, 17-OCH_3), 3.78 (q, *J* = 6.6 Hz, 2 H, 8^{1}-CH_2), 4.37 (dd, *J* = 10.4, 2.3 Hz, 1 H, 17-CH), 4.45 (q, *J* = 7.3 Hz, 1 H, 18-CH), 4.85 (dd, *J* = 15.3, 4.9 Hz, 1 H, 13^{2}-CH_2), 5.04 (dd, *J* = 15.3, 4.9 Hz, 1 H, 13^{2}-CH_2), 5.26 (d, *J* = 18.8 Hz, 1 H, 15^{1}-CH_2), 5.52 (d, *J* = 18.8 Hz, 1 H, 15^{1}-CH_2), 6.14 (dd, *J* = 11.6, 1.1 Hz, 1 H, 3^{2}-C=CH_2), 6.35 (dd, *J* = 11.6, 1.1 Hz, 1 H, 3^{2}-C=CH_2), 6.42 (dd, *J* = 3.3, 1.8 Hz, 1 H, 13^{2}-ArH), 6.49 (d, *J* = 2.9 Hz, 1 H, 13^{7}-ArH), 6.75 (t, *J* = 5.3 Hz, 1 H, 13^{2}-NH), 7.49 (dd, *J* = 1.8, 0.8 Hz, 1 H, 13^{8}-ArH), 8.08 (dd, *J* = 18.1, 11.5 Hz, 1 H, 3^{1}-CH=), 8.79 (s, 1 H, 20-H), 9.62 (s, 1 H, 5-H), 9.68 (s, 1 H, 10-H).
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