Chemical Transformations of the Vinyl Group in Natural Chlorins. The Synthesis of 3–Azidomethylchlorins

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Transformation of 3-vinylchlorins into azidomethyl-derivatives was investigated for chlorin p, trimethyl ester. The azide group allows modifying chlorophyll derivatives on pyrrole ring A by the use of “click reaction” with terminal alkynes. As an example, reaction with phenylacetylene was carried out.

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Figure 1. Synthesis of chlorin $p_3$ azide derivative.

Figure 2. Click reaction.

Further modification of molecule by substituents of different nature, affecting the physico-chemical properties of new PS and their tropism to malignant tumors. The vinyl group in chlorin $p_3$ was oxidized to aldehyde (2) by osmium tetroxide in the presence of sodium periodate (Figure 1).

Next, the aldehyde group was reduced to alcohol. In the literature, the complex of tert-butylamine and borane or sodium cyanoborohydride is most frequently used for reduction of 3-formylchlorins with average yields. Here, we managed to reduce the aldehyde group in chlorin (2) using solid sodium borohydride in aqueous THF with excellent yield.

Thereafter, a one-step conversion of alcohol to azide was performed. It is known that reaction of bis(p-nitropheryl)phosphorazidate in the presence of DBU with aliphatic alcohols leads to formation of alkylazides. In our case, the alcohol (3) was mixed with excess of $p$-NO$_2$DPPA and DBU in toluene to obtain azide (4). The reaction was fully completed in 10 min at room temperature with 88 % yield. The structure of the compound was confirmed by $^1$H NMR spectrum and high-resolution mass spectrum.

Resulting azide (4) easily enters to “click reaction” with compounds containing a terminal acetylene group (Figure 2). Model synthesis was carried out in DMF on a zinc complex of chlorin (4) with phenylacetylene in the presence of copper(I) iodide as a catalyst. The reaction yield was 75 %.

Thus, the reported here method of preparation of 3-azidomethylchlorins opens up new possibilities for modification of natural chlorins in pyrrole ring A and the development of new potential photosensitizers for PDT.

**Experimental**

Sodium periodate, sodium borohydride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from Sigma-Aldrich company. Chlorin $p_3$ trimethyl ester, bis(p-nitropheryl)phosphorazidate were prepared according to reported procedures. Column chromatography and preparative TLC was performed on silica gel (Merck, Kieselgel 60, 40–63 μm, and 5–40 μm, respectively). UV-Visible absorption spectra were taken on a Shimadzu UV-1800 spectrophotometer. $^1$H NMR spectra were obtained on a 300 MHz Bruker DPX-300 spectrometer. High resolution mass spectra (HRMS) were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI).

$3$-Devinyl-3-formylchlorin $p_3$ trimethyl ester (2). Chlorin $p_3$ trimethyl ester (1) (100 mg, 0.156 mmol) was dissolved in 20 ml of THF, 5 ml of 10 % aqueous solution of sodium periodate and 5 % solution of osmium tetroxide in dichloromethane (40 μl, 0.0079 mmol) was added. The solution was stirred for 1.5 h at room temperature in argon atmosphere. The mixture was diluted with 100 ml of dichloromethane and washed with water. Organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by silica gel column chromatography (CHCl$_3$-MeOH, 60:1). Yield: 84 mg (85 %).
UV-Vis (CH₃Cl) \( \lambda_{max} \) (\( \varepsilon/dm^3mol^{-1}cm^{-1} \)) nm: 699.0 (42600), 639.5 (6300), 544.5 (9000), 508.0 (7900), 412.5 (123600). \(^{1}H\) NMR (300 MHz, CDCl \(_3\) \( \delta\) ppm: 11.45 (s, 1H, -CHO), 10.19 (s, 1H, 10-H), 9.68 (s, 1H, 5-H), 8.84 (s, 1H, 20-H), 5.19 (d, \( J = 9.1\) Hz, 1H, 18-H), 4.46 (m, 1H, 17-H), 4.27 (s, 3H, 13-CO \(_2\)CH₃), 4.21 (s, 3H, 13-CO \(_2\)CH₃), 3.73 (s, 3H, 12-CH₃), 3.71 (q, \( J = 7.6\) Hz, 2H, -CH\(_2\)-CH₃), 3.66 (s, 3H, -CH₂-), 3.57 (s, 3H, 7-CH₃), 3.26 (s, 3H, 17-CO \(_2\)CH₃), 2.46 (m, 1H, 17-H), 2.25 (m, 1H, 17-H), 2.14 (m, 1H, 17-H), 1.93 (m, 1H, 17-H), 1.88 (d, \( J = 7.2\) Hz, 2H, 18-CH₃), 1.69 (s, \( J = 7.6\) Hz, 3H, -CH\(_3\)-CH₂-), -0.86 and -1.36 (2bs, 2H, NH).

3-Devinyl-3-(4-phenyl-1,2,3-triazole-1-yl)methyl chlorin p₆ trimethyl ester (3). Chlorin (2) (70 mg, 0.082 mmol) was dissolved in a mixture of 20 ml of THF and 20 ml of water. 3 mg of sodium borohydride (0.026 mmol) was added over 2 h. The mixture was diluted with 200 ml of dichloromethane and washed twice with water. The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. The chlorin (3) was recrystallized from THF:heptane system (1:5). Yield: 63 mg (90 %). HRMS (ESI) \( m/z \) m/z: 664.3060, 609.5 (5600), 526.5 (4700), 496.5 (127400). 1H NMR (300 MHz, CDCl \(_3\) \( \delta\) ppm: 9.77 (s, 1H, 10-H), 9.47 (s, 1H, 5-H), 8.78 (s, 1H, 20-H), 7.64 (m, 2H, Ph-H), 7.61 (s, 1H, triazole-H), 7.23 (m, 3H, Ph-H), 6.86 (s, 2H, 3'-CH₃), 5.21 (d, \( J = 6.2\) Hz, 1H, 18-H), 4.45 (m, 1H, 17-H), 4.26 (s, 3H, 13-CO \(_2\)CH₃), 4.20 (s, 3H, 15-CO \(_2\)CH₃), 3.75 (q, \( J = 7.6\) Hz, 2H, -CH\(_2\)-CH₃), 3.68 (s, 3H, 12-CH₃), 3.55 (s, 3H, 2-CH₃), 3.47 (s, 3H, 7-CH₃), 3.25 (s, 3H, 17-CO \(_2\)CH₃), 2.42 (m, 1H, 17-H), 2.24 (m, 1H, 17-H), 2.09 (m, 1H, 17-H), 1.90 (m, 1H, 17-H), 1.88 (d, \( J = 7.2\) Hz, 3H, 18-CH₃), 1.65 (t, \( J = 7.6\) Hz, 3H, -CH\(_3\)-CH₂-), -1.14 (2bs, 2H, NH).

3-Devinyl-3-azidomethylchlorin p₆ trimethyl ester (4). Hydrochlorin (3) (50 mg, 0.049 mmol) was dissolved in 5 ml of toluene, 32 mg (0.1 mmol) of bis(p-nitrophenyl)phosphorazidate and 16 \( \mu \)l (0.1 mmol) of DBU were added. Mixture was stirred at a room temperature for 10 min in argon atmosphere. Solvent was evaporated, product was dissolved in 50 ml of dichloromethane, washed with water followed by 30 ml of 0.5 % HCl aqueous solution and water. Then solution was dried over anhydrous sodium sulfate and evaporated to dryness. Chlorin (4) was purified by silica gel column chromatography (CHCl₃:MeOH, 40:1). Yield 31 mg (75 %). UV-Vis (CH₃Cl) \( \lambda_{max} \) (\( \varepsilon/dm^3mol^{-1}cm^{-1} \)) nm: 664.3031, calcd for C \(_{35}\)H \(_{39}\)N \(_{7}\)O \(_{6}\) 654.3031, calcd for C \(_{35}\)H \(_{39}\)N \(_{7}\)O \(_{6}\) 654.3031. \(^{1}H\) NMR (300 MHz, CDCl \(_3\) \( \delta\) ppm: 11.45 (s, 1H, -CHO), 10.19 (s, 1H, 10-H), 9.34 (s, 1H, 5-H), 8.65 (s, 1H, 20-H), 5.62 (s, 2H, CH \(_2\)OH), 5.20 (d, \( J = 9\) Hz, 1H, 18-H), 4.42 (m, 1H, 17-H), 4.25 (s, 3H, 13-CO \(_2\)CH₃), 4.19 (s, 3H, 15-CO \(_2\)CH₃), 3.63 (q, \( J = 7.6\) Hz, 2H, -CH\(_2\)-CH₃), 3.62 (s, 3H, 12-CH₃), 3.54 (s, 3H, 2-CH₃), 3.29 (s, 3H, 7-CH₃), 3.14 (s, 3H, 17-CO \(_2\)CH₃), 2.41 (m, 1H, 17-H), 2.24 (m, 1H, 17-H), 2.08 (m, 1H, 17-H), 1.90 (m, 1H, 17-H), 1.88 (d, \( J = 7.2\) Hz, 3H, 18-CH₃), 1.65 (t, \( J = 7.6\) Hz, 3H, -CH\(_3\)-CH₂-), -1.14 (2bs, 2H, NH).

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