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FIRST MACROCYCLE BASED ON CHLORIN AND ISOSTEVIOL STRUCTURAL ELEMENTS

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Acylation by suberic acid chloride of chlorin with two oximated isosteviol groups on its periphery produced for the first time a macrocyclic system containing a porphyrin ring and two tetracyclic ent-*beyerane frameworks.*

Keywords: chlorin e_6, isosteviol, *ent*-beyerane, macrocycle, dioxime, suberic acid chloride.

Macrocyclic compounds are interesting as subjects of supramolecular chemistry for studying intermolecular interactions, molecular recognition phenomena, etc. [1]. Construction of macrocycles based on biologically active compounds can lead to the manifestation of new properties, including enhancement of the biological activity as, for example, in the result of macrocyclization of taxol [2]. The goal of the present work was to synthesize a macrocycle combining the biologically active molecules chlorin e_6 and the diterpenoid isosteviol (16-oxo-*ent*-beyeran-19-oic acid).

Natural and semi-synthetic porphyrins, including chlorin e_6, are currently being investigated as photosensitizers for photodynamic therapy of oncological diseases [2]. The diterpenoid isosteviol exhibits diverse biological activity [3–8] and prevents coronary [8, 9] and cerebral ischemia.

A chlorin with two isosteviol frameworks that was prepared from methylpheophorbide *a* by the literature method [9] was used to construct the macrocycle (Scheme 1). Reaction with hydroxylamine in Py produced dioxime **4**, which was then reacted with suberic acid chloride to form macrocycle **5**. The reaction of **4** with suberic acid chloride was carried out under high-dilution conditions in order to form macrocycle **5** and avoid formation of oligomeric products. It could be assumed that the unusually high yield of **5** was due to not only the high-dilution conditions but also the pre-organization of **4** to formation of the macrocycle, namely, its existence in a conformation with the isosteviol oximes close to each other. The structures of all synthesized compounds were confirmed by PMR spectroscopy and mass spectrometry (MALDI). The PMR spectrum of **4** exhibited resonances for the chlorin macrocycle and two isosteviol frameworks. The PMR spectrum of the resulting macrocycle **5** showed the aforementioned resonances and multiplets for the methylene protons of the suberic group at 1.22–1.07 ppm. The MALDI spectrum of **4** and the product of its reaction with suberic acid chloride contained peaks corresponding to molecular ions for **4** (1325.800 $[M]^+$) and **5** (1463.088 $[M]^+$).

Compound **5** is the first semi-synthetic macrocyclic compound constructed of chlorin and isosteviol (*ent*-beyerane) elements. The study of the properties of **5** and compounds analogous to it will be reported separately.

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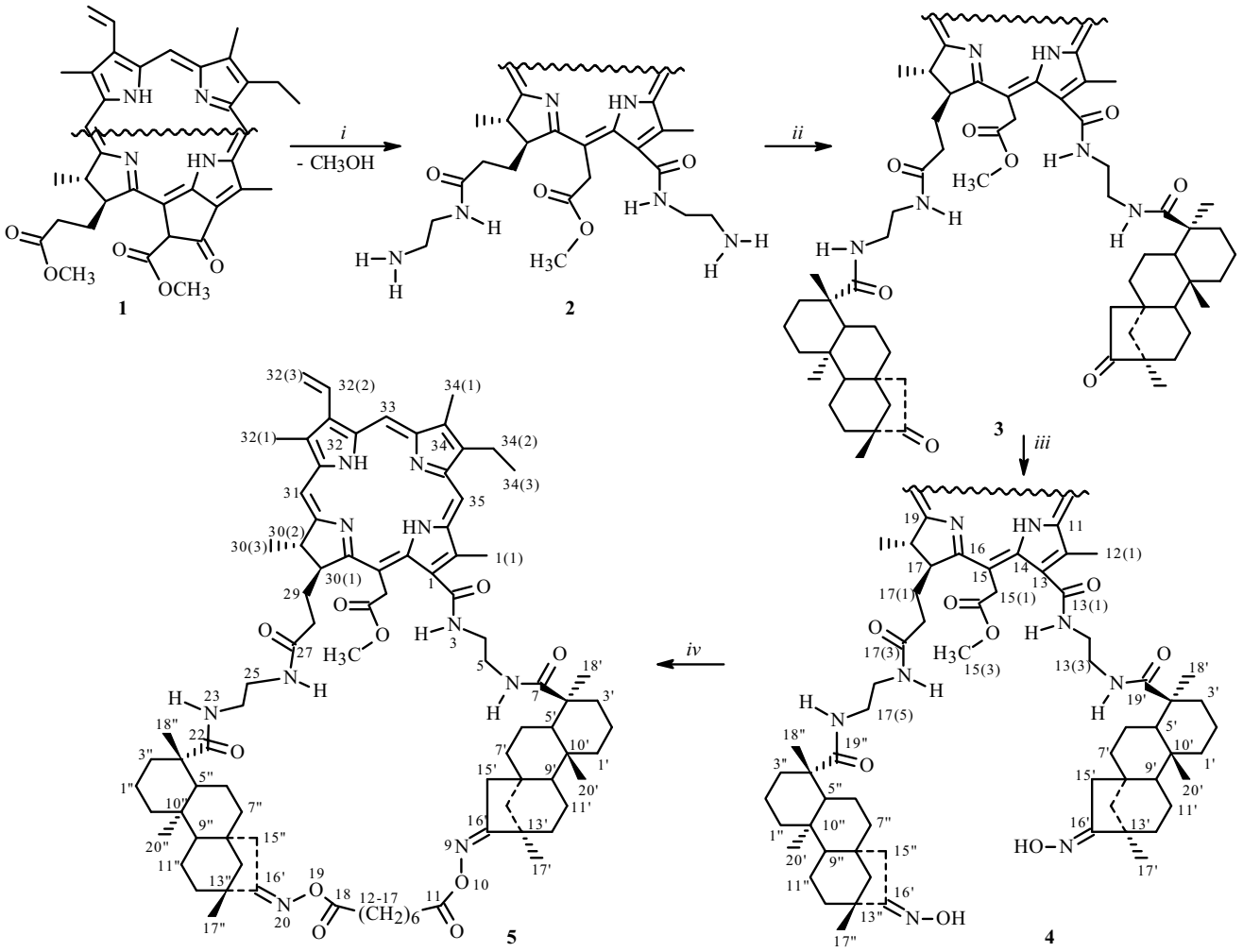

i. $2H_2NCH_2CH_2NH_2$, 24 h, 20°C; *ii*: isosteviol chloride, THF, reflux 2 h, 30% yield; *iii*. $2NH_2OH{\cdot}HCl$, Py, reflux 30 min, 72% yield; *iv*. $ClOC(CH_2)_6COCl$, THF, reflux 1 h, 71% yield.

Scheme 1

EXPERIMENTAL

PMR spectra were recorded in $CDCl_3$ on a Bruker Avance-300 instrument (operating frequency 300 MHz for ^1H). Mass spectra were obtained on a Vision 2000 mass spectrometer (MALDI). Column chromatography used Silica gel 60 (0.060–0.2 mm, 70–230 mesh).

Chlorin e_6 13,17-*N*,*N*′-*bis*(2-(19-Nor-16-oximo-*ent*-beyeran-4α-ylcarbonyl)aminoethyl)-diamide-15-methyl Ester (4). A solution of chlorin **3** (300 mg, 0.23 mmol) in Py (7 mL) was treated with hydroxylamine hydrochloride (300 mg, 4.31 mmol), refluxed for 30 min (TLC monitoring, $CHCl_3$:MeOH, 9:1), diluted with $CHCl_3$ (100 mL), and washed with HCl solution (5%) to remove Py and then H_2O to remove acid. The resulting solution was dried over anhydrous Na_2SO_4 and evaporated. Chromatography over silica gel (CCl_4:acetone, 2:1) afforded **4** (220 mg, 72%) (100% conversion). Mass spectrum (MALDI, *m*/*z*): calc. for $[MH]^+$ ($C_{79}H_{109}N_{10}O_8$): 1325.843; found: 1325.800.

PMR spectrum (DMSO-d_6, 300 MHz, δ, ppm, J/Hz): 10.21 (1H, s, N–OH), 10.13 (1H, s, N–OH), 9.82 (1H, s, 10-H), 9.78 (1H, s, 5-H), 9.14 (1H, s, 20-H); NH amide protons in positions 13(1), 13(3), 17(3), and 17(5): 9.25–9.18 (1H, br.m), 7.92 (1H, br.t, J = 4.0), 7.46 (1H, br.t, J = 6.0), 7.01 (1H, br.t, J = 4.5), 8.35 [1H, dd, J = 17.0, 12.2, 3(1)-H], 6.47 [1H, d, J =18.0, 3(2)-H_{trans}], 6.21 [1H, d, J = 11.7, 3(2)-H_{cis}], 5.56 [1H, d, J = 18.7, 15(1)-H_A], 5.30 [1H, d, J = 19.2, 15(1)-H_B], 4.61 (1H, br.q, J = 7.2, 18-H), 4.38 (1H, br.d, J = 10.2, 17-H), 3.85 [2H, br.q, J = 7.0, 8(1)-H_2], 3.77–3.64 and 3.62–3.48 [8H, m, 13(2)-H_2, 13(3)-H_2, 17(4)-H_2, 17(5)-H_2], 3.70 [3H, s, 15(3)-H_3], 3.55 [3H, s, 12(1)-H_3], 3.52 [3H, s, 2(1)-H_3], 3.34 [3H, s, 7(1)-H_3];

15′-H_α, 15″-H_α: 2.97 (2H, br.d, J = 18.9) and 2.69 (2H, br.d, J = 1.83), 2.50–2.40 and 2.34–2.18 [4H, m, 17(1)-H_2, 17(2)-H_2], 1.69 [3H, t, J = 7.1, 8(2)-H_3], 1.68 [3H, d, J = 6.9, 18(1)-H_3]; 19′-H_3 and 19″-H_3: 1.17 (3H, s) and 1.04 (3H, s); 17′-H_3 and 17″-H_3: 0.98 (3H, s) and 0.95 (3H, s); 20′-H_3 and 20″-H_3: 0.84 (3H, s) and 0.60 (3H, s); 2.18–2.06, 2.00–1.86, 1.85–1.76, 1.64–1.52, 1.46–1.28, 1.26–1.12 (36H, m, *ent*-beyerane framework); –1.82 (1H, br.s, I-NH), –2.09 (1H, br.s, III-NH).

1^1H,31^1H-1,29,31,33(2,5)-Tetrapyrrol-35-methyloxycarboxomethyl-10,19-dioxa-3,6,9,20,23,25-hexaaza-31^3-vinyl-33^3-ethyl-1^4,29^4,31^4,33^4-tetramethyl-1^2(35),1^5(34),8^{16}(9),20(21^{16}),29^5(30),32(33^5)-hexaen-8,21(4,16)-di-*ent*-19-norbeyeran-4α-ylcyclopentatriacontaphan-2,7,11,18,22,27-hexaone (5). Chlorin e_6 13,17-*N*,*N*′-(2-(*N*,*N*′-diisostevioloxime)aminoethyl)-diamide-15-methyl ester (**4**, 200 mg, 0.15 mmol) in THF (150 mL) was refluxed, treated dropwise over 1 h with suberic acid chloride (32 mg, 0.15 mmol) in THF (50 mL), refluxed for another hour (TLC monitoring, $CHCl_3$:MeOH, 9:1), diluted with $CHCl_3$ (50 mL), and washed with H_2O to remove HCl that formed during the reaction. The resulting solution was dried over anhydrous Na_2SO_4, evaporated, and chromatographed over silica gel (CCl_4:acetone, 10:1) to afford **5** (155 mg, 71%) (100% conversion). Mass spectrum (MALDI, *m*/*z*): calc. for $[M]^+$ ($C_{87}H_{118}N_{10}O_{10}$): 1462.903; found: 1463.088.

PMR spectrum (DMSO-d_6, 300 MHz, δ, ppm, J/Hz): 9.80 (1H, s, 35-H), 9.78 (1H, s, 33-H), 9.12 (1H, s, 31-H); N3-H, N6-H, N26-H, and N32-H: 9.18 (1H, br.m), 7.87 (1H, m), 7.52 (1H, m), 7.07 (1H, m), 8.36 [1H, dd, J = 18.2, 11.6, 32(2)-H], 6.49 [1H, d, J = 18.0, 32(3)-H_{trans}], 6.21 [1H, d, J = 12.0, 32(3)-H_{cis}], 5.55 [1H, d, J = 19.0, 36(1)-H_A], 5.27 [1H, d, J = 18.6, 36(1)-H_B], 4.60 [1H, m, 30(2)-H], 4.36 [1H, m, 30(1)-H], 3.85 [2H, m, 34(2)-H_2], 3.80–3.65 (2H, m, 4-H_2), 3.64–3.41 (10H, m, 5-H_2, 25-H_2, 24-H_2, 12″-H_2, 17″-H_2), 3.71 [3H, s, 36(3)-H_3], 3.55 [3H, s, 1(1)-H_3], 3.52 [3H, s, 32(1)-H_3], 3.37 [3H, s, 34(1)-H_3], 2.97–2.63 (2H, m, 15′-H_α, 15″-H_α), 2.58–2.35 (4H, m, 28-H_2, 29-H_2), 1.69 [3H, t, J = 7.4, 34(3)-H_3], 1.68 [3H, d, J = 7.2, 30(3)-H_3]; 18′-H_3 and 18″-H_3: 1.18 (3H, s) and 1.12 (3H, s); 17′-H_3 and 17″-H_3: 1.03 (3H, s) and 0.99 (3H, s); 20′-H_3 and 20″-H_3: 0.86 (3H, s) and 0.44 (3H, s); *ent*-beyerane framework and suberic protons 13″-H_2, 14″-H_2, 15″-H_2, and 16″-H_2: 2.35–2.27 (3H, m), 2.19–2.08 (5H, m), 2.01–1.89 (6H, m), 1.59–1.38 (14H, m), 1.33–1.23 (8H, m), 1.22–1.07 (10H, m); –1.80 (1H, br.s, N32-H), –2.09 (1H, br.s, N1-H).

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