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Synthesis of the conjugate of *ortho*-isobornylphenol with pheophorbide (a)

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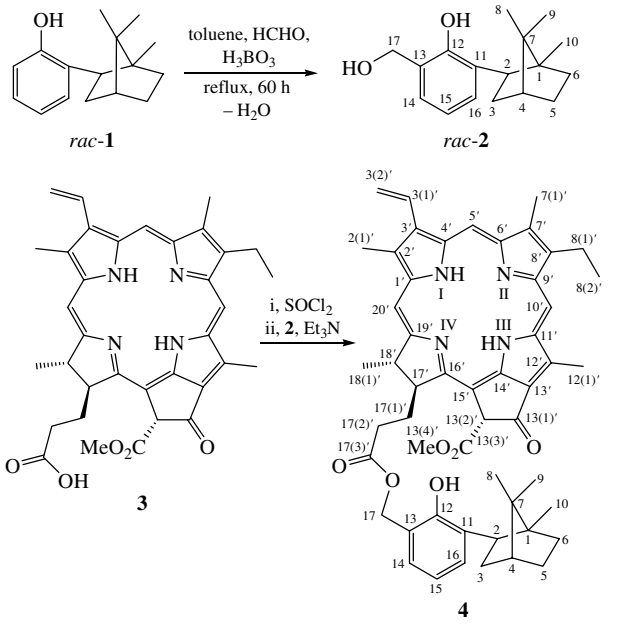
The introduction of a terpenophenolic fragment to the periphery of a chlorin cycle has been carried out.

Terpenophenolic compounds are physiologically active substances with a wide range of activity (radioprotectors, anticancer prophylactic preparations, electron carriers in respiratory chain, psychotropic compounds, growth inhibitors of pathogenous fungi, exogenous and endogenous antioxidants, hepathoprotectors, *etc.*).[1–3] Chlorophyll derivatives are the acting substances of a number of antitumour preparations (*e.g.*, photosensitizers) and can be used in the therapy of viral diseases.[4,5] The combinations of some pharmacophoric groups in one molecule can lead to intensification of the known physiological activity and also to a new one. Thus, the introduction of a terpene fragment to the periphery of a chlorin cycle can increase the ability of porphyrins to interact with cell membranes. We performed the introduction of a terpenophenolic fragment to the periphery of a chlorin cycle. Racemic *ortho*-isobornylphenol **1** was prepared earlier[6] and alcohol **2** was synthesised by the known method.[7] The interaction of **2** with the activated carboxylic group of pheophorbide (a) **3** leads to **4** (Scheme 1).

In the ^{1}H NMR spectrum of compound **4**, the signals corresponding to both chlorin and terpenophenolic fragments are observed. The absence of the hydrogen atom signal of the alcohol hydroxyl group allows one to conclude, that this hydroxyl group has joined the reaction. In the ^{1}H NMR spectrum of **4**, the signals of chlorin fragment protons, the chemical shift of



Scheme 1 Synthesis of the conjugate of *ortho*-isobornylphenol with pheophorbide (a).

which depends on the nature of the substituent at the $C^{17'}$ position of chlorin cycle, are 'decomposed' (proton signals $C^{20'}H$, $C^{13(4)'}H_3$, $C^{18(1)'}H_3$).

Analogous 'doubling' of signals is observed for a number of terpenophenolic fragment protons ($C^{17}H_2$; HO–C^{12}; one of the signals of the terpene Me groups). Spectral peculiarities mentioned above can be explained by the fact that initial compound **1** is a mixture of two enantiomers; therefore, conjugate **4** is a mixture of diastereomers, as revealed in the ^{1}H NMR spectrum.†

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† ^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX-400 (400 MHz) and Bruker AM-300 (300 MHz) spectrometers in $CDCl_3$. The IR spectra were recorded on Specord M80 (KBr pellets). Compound **3** was obtained from the nettle.[8] Spectral characteristics of **3** are consistent with those described previously.[9]

Rac-*2-(hydroxymethyl)-6-*(exo-*1,7,7-trimethylbicyclo[2.2.1]hept-2yl)phenol rac*-**2**. A mixture of 2.0 g (8.7 mmol) of *ortho*-isobornylphenol **1**, 0.87 g (13.3 mmol) of boric acid and 0.4 g (13.3 mmol) of paraform in 30 ml of toluene was boiled in a flask equipped with a Dean-Stark nozzle on continuous water removal as an azeotrope for 60 h; 0.1 g (3.3 mmol) of paraform was added periodically each 4 h. After the reaction was completed, the excess of toluene was removed at a lower pressure. To a residue 30 ml of water was added, and it was kept for 12 h to perform the hydrolysis of the intermediate borosalicylic ester. Extraction was carried out by diethyl ether (3×20 ml), the combined ether fractions were washed with water (30 ml), the solvent was removed at lower pressure, chromatography was carried out on a column (La Chema silica gel, 100–200 mesh, eluent, petroleum ether–diethyl ether). A fraction containing **2** was evaporated at lower pressure and after evaporation the residue was recrystallised from hexane to give 1.55 g (71%) of alcohol **2** as colourless crystals, mp 80–84 °C. IR (KBr, ν/cm^{-1}): 3438 (OH phenol), 3596 (OH alcohol), 1183 (C–O), 2951, 2876, 1456 (Me, CH_2), 3029, 758 (=C–H), 1595 (C=C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.81 (s, $C^{10}H_3$), 0.87 (s, C^9H_3), 0.93 (s, C^8H_3), 1.36–1.43 (m, C^5H), 1.50–1.70 (m, C^3H, C^6H_2), 1.86–1.88 (m, C^5H, C^4H), 2.15–2.24 (m, C^3H), 2.44 (br. t, HO–C^{17}), 3.30 (t, C^2H, J 8.9 Hz), 4.75 (dd, $C^{17}H$, J 3.7 and 12.7 Hz), 4.89 (dd, $C^{17}H$, J 4.6 and 12.7 Hz), 6.81–6.88 (m, $C^{14}H$, $C^{16}H$), 7.31 (dd, $C^{15}H$, J 1.6 and 7.1 Hz), 7.51 (s, HO–C^{12}). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 12.30 (C^{10}), 20.33 (C^9), 21.40 (C^8), 27.47 (C^5), 33.99 (C^3), 39.71 (C^6), 44.82 (C^2), 45.60 (C^4), 47.91 (C^7), 49.79 (C^1), 64.98 (C^{17}), 118.94 (C^{16}), 123.74 (C^{13}), 125.07 (C^{14}), 128.15 (C^{15}), 131.25 (C^{11}), 155.37 (C^{12}). Found (%): C, 78.72; H, 9.37. Calc. for $C_{17}H_{24}O_2$ (%): C, 78.42; H, 9.29.

Pheophorbide (a) 17-{2-hydroxy-3-(exo-*1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl)benzylic} ester* **4**. Compound **3** (0.25 g, 0.42 mmol) was dissolved in 2 ml of freshly distilled thionyl chloride, the solution obtained was dry evaporated in a vacuum at 30 °C. After evaporation, the residue was dissolved in 5 ml of CH_2Cl_2 and to this solution 0.5 ml of triethylamine and 0.33 g (1.27 mmol) of **2** dissolved in 2 ml of CH_2Cl_2 were added. The mixture was stirred at room temperature for 8 h. Product **4** was purified by column chromatography on silica gel (Alfa Aesar, 70–230 mesh), eluted by petroleum ether–diethyl ether (5:1) and then CCl_4–acetone (from 20:1 to 5:1), the fraction containing **4** was evaporated at lower pressure and after evaporation the residue was reprecipitated with pentane from chloroform to give 0.12 g (46%) of conjugate **4** as dark-green crystals, mp 123–125 °C (decomp.). IR (KBr, ν/cm^{-1}): 1624 ('chlorin band'), 1746 (C=O ester), 1706 (C=O keto group in exocycle). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: terpenophenolic fragment, 0.67 / 0.68 (s, 3H, $C^{10}H_3$) (two diastereomers, 1:1), 0.79 (s, 3H, C^9H_3), 0.81 (s, 3H, C^8H_3), 1.4–1.6 (m), 1.8–1.9 (m), 2.00–2.68 (m, 6H, C^3H_2, C^5H_2 and C^6H_2), 3.24–3.30 (m, 2H, C^2H and C^4H), 4.89 and 5.07 (2d, 2×1H, $C^{17}H_2$, J 12.2 Hz) / 4.94 and 5.16 (2d, 2×1H, $C^{17}H_2$, J 12.4 Hz) (two diastereomers, 1:1), 6.76–6.81 (m), 6.95–6.98 (m, 2H, $C^{14}H$ and $C^{16}H$), 7.27–7.30 (m, 1H, $C^{15}H$), 7.72 / 7.73 (s, 1H, HO–C^{12}) (two diastereomers, 1:1); *chlorin fragment*, –1.46 (br. s, 1H, $N^{III}H$), 0.51 (br. s, 1H, $N^{I}H$), 1.69 (t, 3H, $C^{8(2)'}H_3$, 7.6 Hz), 1.74 (d, 3H, $C^{18(1)'}H_3$, 7.2 Hz) / 1.76 (d, 3H, $C^{18(1)'}H_3$, J 7.2 Hz) (two diastereomers, 1:1), 2.00–2.68 (m, 4H, $C^{17(1)'}H_2$ and $C^{17(2)'}H_2$), 3.22 (s, 3H, $C^{7(1)'}H_3$), 3.39 (s, 3H, $C^{2(1)'}H_3$), 3.62–3.71 (m, 2H, $C^{8(1)'}H_2$), 3.68 (s, 3H, $C^{12(1)'}H_3$), 3.87 / 3.88 (s, 3H, $C^{13(4)'}H_3$) (two diastereomers, 1:1), 4.15–4.50 (m, 2H, $C^{17'}H$ and $C^{18'}H$), 6.17 (d, 1H, $C^{3(2)'_{cis}}H$, J 11.2 Hz), 6.23 (s, 1H, $C^{13(2)'}H$), 6.28 (d, 1H, $C^{3(2)'_{trans}}H$, J 17.2 Hz), 7.98 (dd, 1H, $C^{3(1)'}H$, J 17.2 and 11.6 Hz), 8.50 / 8.52 (s, 1H, $C^{20'}H$) (two diastereomers, 1:1), 9.37 (s, 1H, $C^{5'}H$), 9.51 (s, 1H, $C^{10'}H$). Found (%): C, 74.32; H, 7.27; N, 6.34. Calc. for $C_{52}H_{58}N_4O_6$ (%): C, 74.79; H, 7.00; N, 6.71.