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Synthesis of Azaspirographis Porphyrin and its Transformation into an Azachlorin

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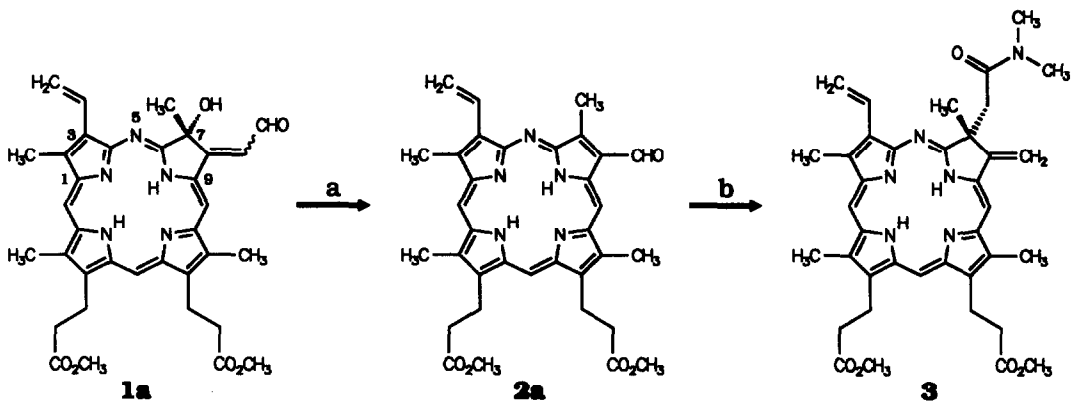
Abstract: Azaspirographis porphyrins **2a** and **2b** were prepared as precursors for the synthesis of geminally dialkylated azachlorins, a new class of potential long wavelength photosensitizers for photodynamic therapy of cancer.

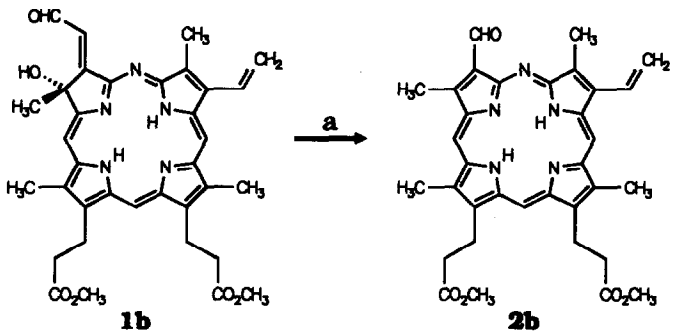
We have previously reported on the preparation of azachlorins **1a,b** starting from the naturally occurring bile pigment bilirubin[1]. The photophysical properties of this novel structural type with a nitrogen atom instead of a methine unit in the chlorin framework recommend these pigments for an application in photodynamic therapy (PDT) of cancer. The azachlorins **1a,b** are quite sensitive to traces of acid which induce rearrangement and elimination reactions to form undefined mixtures of products.

To obtain more stable azachlorins suitable for an application in PDT we aimed at the synthesis of the azachlorin **3**, in which the geminally dialkylated structural part of the partially saturated pyrrole ring prevents the azachlorin from decomposition and other undesired reactions.



scheme 1: a) 1. $NaBH_4$, CH_2Cl_2, MeOH, room temp. 5 min. 2. H_2SO_4, $NaIO_4$, CH_2Cl_2, THF, H_2O, room temp., 6 h. b) 1. $NaBH_4$, CH_2Cl_2, MeOH, room temp., 5 min. 2. $MeC(OMe)_2NMe_2$, o-xylene, 80°C, 1 h then reflux, 3 h.

The E,Z-isomeric mixture **1a** was transformed into one of the 5-aza-analogues of the two constitutionally isomeric spirographis porphyrins[2], which contain the usual methine unit instead of the nitrogen atom. After reduction of the aldehyde function of **1a** the 7-hydroxyl group of the newly formed diol underwent acid catalyzed allylic rearrangement to form the corresponding porphinyl glycol. The glycol was cleaved *in situ* with sodium periodate to yield the aldehyde **2a**. The same reaction sequence was applied to the chlorin isomer **1b** to obtain the 5-aza-analogue **2b** of the naturally occurring spirographis porphyrin[2].



1b **2b**

scheme 2: a) 1. $NaBH_4$, CH_2Cl_2, MeOH, room temp., 5 min. 2. H_2SO_4, $NaIO_4$, CH_2Cl_2, THF, H_2O, room temp., 2 h.

The preparation of the geminally dialkylated azachlorin **3** was achieved by sodium borohydride reduction of the aldehyde function in **2a** followed by amide acetal Claisen rearrangement of the allylic alcohol intermediate.[3,4] On the photophysical and biological properties of geminally dialkylated azachlorins will be reported elsewhere.

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[5] **Analytical Data** *(the represented formula pictures describe racemic mixtures)* :

2a: $C_{34}H_{35}N_5O_5$. m.w. 593.68. **m.p.** 196-198°C. **UV/Vis**($CHCl_3$): λ(ε)= 411(104000), 564(24000), 573(22000), 627(10000). **IR**(KBr): ν = 3290 cm^{-1}(vw, νNH), 2940, 2900, 2840(w, νCH), 1725(s, νCO, ester), 1650(s, νCO, aldehyde), 1560(vw, νCN, CC), 1430, 1375, 1340(m), 1270, 1255, 1240(w), 1195,1160(m), 1105, 1070, 1050, 1020, 1010, 990, 980(vw), 910, 870, 830, 810(w), 730, 700, 670(m). **^{1}H-NMR**($CDCl_3$): δ= -3.10 ppm(s, 2H, NH), 3.19-3.28(2t, 4H, CH_2CO_2R), 3.49, 3.65, 3.76 and 3.92(4s, 12H, 2,7,12,18-methyl), 3.62 and 3.66(2s, 6H, estermethyl), 4.23-4.29 and 4.36-4.43(2t, 4H, $CH_2CH_2CO_2R$), 6.26-6.30, 6.50-6.59 and 8.20-8.30(3dd, 3H, 3-vinyl), 9.98, 10.06 and 10.90(3s, 3H, 10,15,20-methine), 11.40(s, 1H, CHO).**MS**(EI, 70eV, 230°C): *m/z*(%)= 593(100)[M^+], 562(2)[M^+-OCH_3], 520(12)[M^+-$CH_2CO_2CH_3$].

2b: $C_{34}H_{35}N_5O_5$. m.w. 593.68. **m.p.** 228-231°C. **UV/Vis**($CHCl_3$): λ(ε)= 407 nm(48000), 560(10000), 567(sh.,8500), 624(6000), 640(4500). **IR**(KBr): ν = 3290 cm^{-1}(w, νNH), 2940, 2900, 2830(w, νCH), 1730(s, νCO, ester), 1655(s, νCO, aldehyde), 1515(vw, νCN,CC), 1460(m), 1425(w), 1350, 1365, 1330(vw), 1260, 1215, 1190, 1160, 1050(w), 1020, 960, 920, 845, 835(vw), 735, 680(w). **^{1}H-NMR** ($CDCl_3$): δ= -2.30 ppm(s, 2H, NH), 3.25-3.35(2t, 4H, CH_2CO_2R), 3.40, 3.50, 3.66 and 3.83(4s, 12H, 2,7,12,18-methyl), 3.69 and 3.70(2s, 6H, estermethyl), 4.20-4.26(t, 4H, $CH_2CH_2CO_2R$), 6.30-6.33, 6.36-6.43 and 7.95-8.03(3dd, 3H, 8-vinyl), 10.05, 10.18 and 10.92(3s, 3H, 10,15,20-methine), 11.80(s, 1H, CHO). **MS**(EI, 70eV, 250°C): *m/z*(%)= 593(100) [M^+], 565(68)[M^+-CO], 492(16)[M^+-CO -$CH_2CO_2CH_3$].

3: $C_{38}H_{44}N_6O_5$. m.w. 664.80. **m.p.** 160-162°C. **UV/Vis**($CHCl_3$): λ(ε)= 398(125000), 501(7500), 538(16000), 611(6500), 669(57000). **IR**(KBr): ν = 3350 cm^{-1} (w, νNH), 2950, 2940, 2870(w, νCH), 1735(s, νCO, ester), 1635(s, νCO, amide), 1560, 1525(vw, νCN,CC), 1440, 1350, 1290, 1275, 1245. 1230(m), 1160, 1115(w), 1085, 1040, 950, 920, 880, 855, 770(w), 730, 675(m). **^{1}H-NMR**($CDCl_3$): δ= -0.95 ppm(s, 2H, NH), 1.98(s, 3H, 7-methyl), 2.55 and 3.00 (2s, 6H, amidemethyl), 3.08-3.13 and 3.13-3.17(2t, 4H, CH_2CO_2R), 3.41-3.46 and 4.02-4.07(2d, *J*=16Hz, CH_2CONMe_2), 3.30, 3.37 and 3.49 (3s, 9H, 2,12,18-methyl), 3.64 and 3.66 (2s, 6H, estermethyl), 4.04-4.10 and 4.19-4.25(2t, 4H, $CH_2CH_2CO_2R$), 5.79-5.80 and 6.79-6.80(2d, *J*=0.7Hz, 8-methylidene), 6.08-6.13, 6.34-6.40 and 8.05-8.17(3dd, 3H, 3-vinyl), 9.25, 9.52 and 9.64(3s, 3H, 10,15,20-methine). **MS**(EI, 70eV, 230°C): *m/z*(%)= 664(100)[M^+], 578(47)[M^+-$CH_2C(O)N(CH_3)_2$].

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