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SYNTHESIS OF NEW LONG RED ABSORBING PORPHYRINS: REACTIONS OF ORGANOLITHIUMS ON OCTAETHYLPORPHYRINONE.

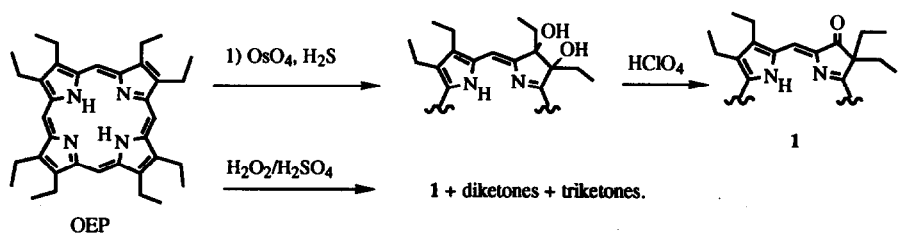
Avinash S. Phadke, Carolynn Butler, Byron C. Robinson and Alan R. Morgan*

Department of Chemistry, University of Toledo, Toledo, OH 43606.

Abstract: *Reaction of Organo lithiums with Porphyrinone 1, after further manipulations afforded porphyrin derivatives absorbing in the range of 690–860 nm.*

Photodynamic therapy (PDT) is an evolving modality for the treatment of cancer. This therapy involves administering a sensitizer which localizes or is retained preferentially in the tumor, followed by irradiation with light of a particular wavelength, to cause tumor necrosis. Optimum penetration of tissue by light is observed between 650-860 nm, and hence sensitizers absorbing strongly in that region are preferred for PDT. Photofrin, a hematoporphyrin derivative is currently used clinically for PDT, and has shown promising results. Unfortunately it absorbs weakly at 620 nm and is not a pure single compound but rather a mixture of monomers, dimers and oligomers of hematoporphyrin. This has prompted workers all over the world to synthesize second generation sensitizers, which are pure single compounds with well established structures, e.g. SnEt2,[1] BPD,[2] NPe_6[3] and others.[4]

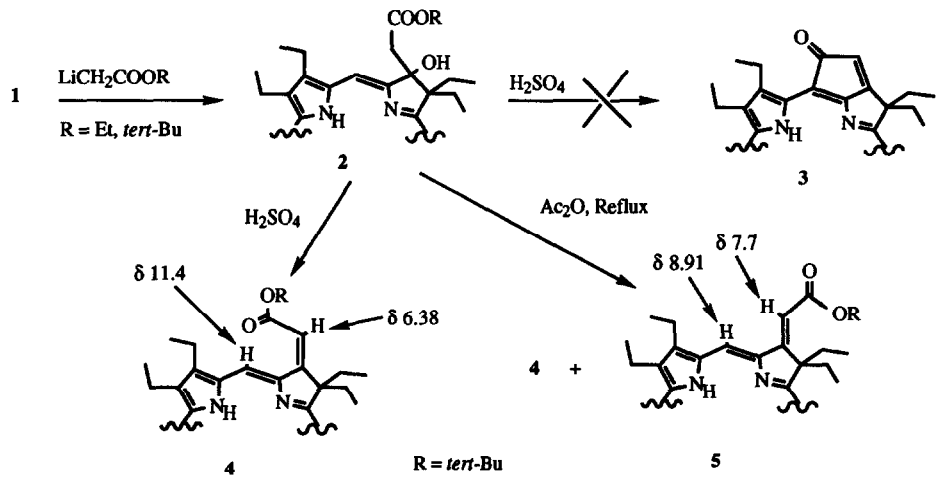
Porphyrinone (1) has a chlorin structure (dihydroporphyrin) which absorbs at 642 nm. Extending the conjugation by introducing a double bond at the position of the carbonyl group further shifts the absorption into the red region, as shown by many workers.[5] Following the same strategy it should be possible to synthesize many porphyrin derivatives absorbing in the range of 690 to 860 nm. Porphyrinone (1) can be prepared by two



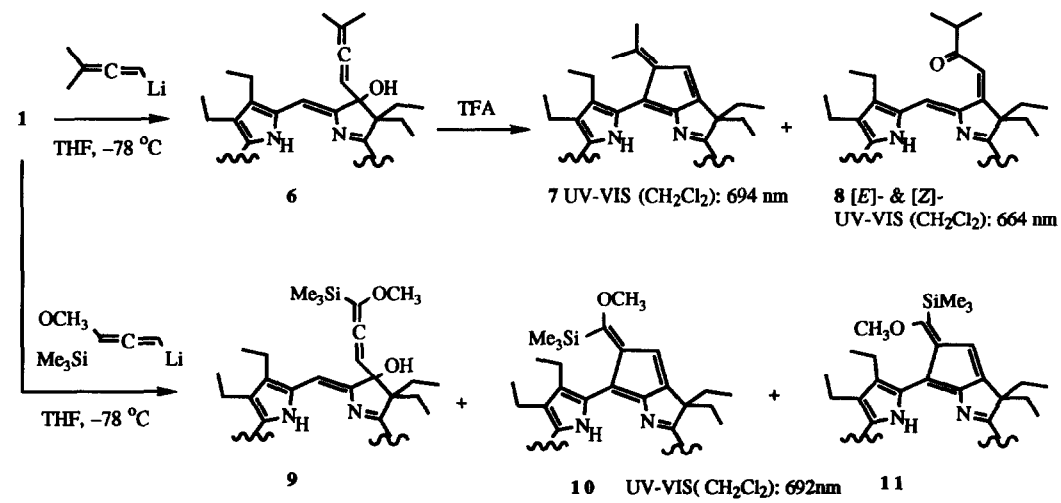
procedures,[6] (a) reaction of octaethyl porphyrin (OEP) with H_2O_2 in the presence of concentrated H_2SO_4, which gives a mixture of porphyrinone (1), and diketones and triketones which can be separated easily; and (b) reaction of OEP with an equivalent amount of osmium tetroxide/H_2S which affords the corresponding diol. Rearrangement in acid then gives the porphyrinone (1) exclusively.

Porphyrinone (1) was treated with preformed alkyl lithio acetate at –78 °C to give the corresponding

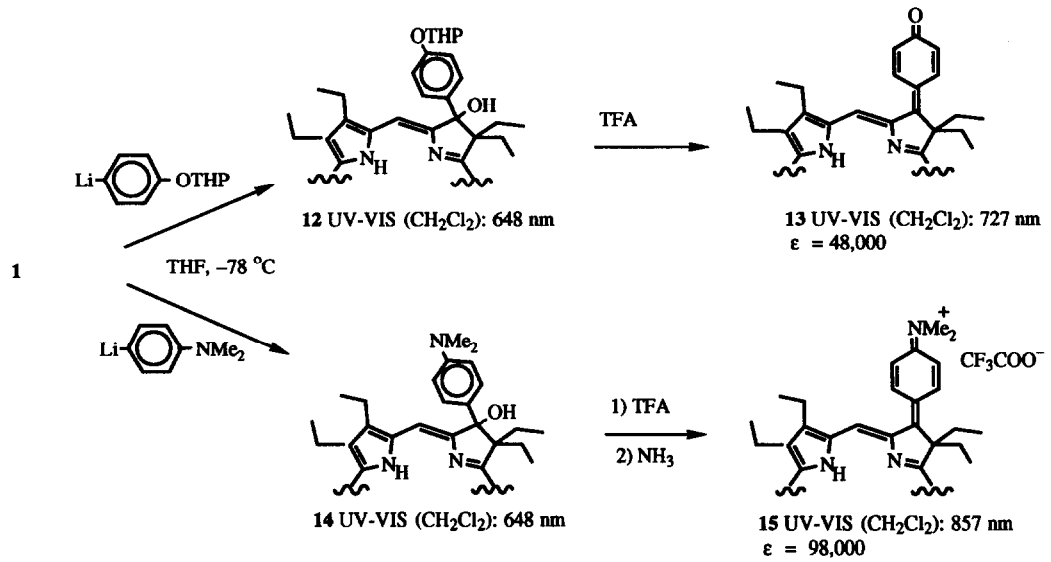
hydroxyl compound (**2**) in very good yields (75-80%).[7] Attempts to cyclize the hydroxyl compound into a purpurin type compound (**3**) using concentrated H_2SO_4 failed, instead affording the dehydrated product (**4**). The presence of only one isomer was confirmed by the NMR spectrum of the dehydrated product. The meso proton closest to the carbonyl of the ester was deshielded and appeared at δ 11.4. When the hydroxy compound was refluxed in acetic anhydride, a mixture of the [*E*]- and the [*Z*]-isomers of the dehydrated product (**4, 5**) was obtained. This again was confirmed by NMR.



Reaction of 1-lithio-3,3-dimethyl allene[8] with porphyrinone (**1**) in THF at –78 °C gave the hydroxyl compound (**6**) in 80% yield. Cyclization in trifluroacetic acid gave the purpurin type product (**7**) in 30% yield, and which gave a typical purpurin visible spectrum with a strong absorption at 694 nm. The remainder of the



product was the [*E*]- and the [*Z*]- isomers of (**8**). The reaction of 1-lithio-3-methoxy-3-trimethyl silyl allene[9] with the porphyrinone (**1**) in THF at –78 °C gave a mixture of the hydroxyl product (**9**, 60%) and the cyclized product (**10**, **11**,40%) which were easily separated by chromatography on silica gel. Cyclization of the hydroxyl compound was not attempted. The cyclized product was again a mixture of the [*E*] and the [*Z*] isomers, which was confirmed by the presence of two singlets each for $\underline{Me_3}Si$–, $C\underline{H_3}O$– and the meso–$\underline{H}$ in the NMR.



4-Lithio tetrahydropyranyl phenol was prepared by metal halogen exchange of 4-bromo tetrahydropyranyl phenol with n-BuLi in THF at -78 °C. This was then reacted with porphyrinone (**1**) at -78 °C. The hydroxyl compound (**12**) was obtained in 80% yield. It was then treated with TFA to afford the quinone derivative (**13**). This compound showed a strong absorption at 728 nm in CH_2Cl_2 (ε= 48,000). The absorption showed dependence on the solvent used, confirming the presence of a quinone. In $CHCl_3$ a red shift to 740 nm was observed while in methanol a further shift to 758 nm was seen. Reaction with 4-lithio N,N-dimethyl aniline gave the hydroxyl product (**14**) in good yields. Treatment of compound **14** in TFA followed by neutralization with ammonia gas afforded the ammonium salt (**15**) in 25% yield. This showed a very strong absorption at 857 nm in CH_2Cl_2 (ε = 98,000), which was also solvent dependent ($CHCl_3$ = 862nm, MeOH = 852nm).

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SPECTROSCOPIC DATA:

4 NMR($CDCl_3$): δ 0.2 (t, 6H, $C\underline{H}_3CH_2$–) , 1.79 (s &m at the base, 27H, $(C\underline{H}_3)_3C$– and $\underline{CH}_3CH_2$–Ar), 2.3 , 2.82 (2m, 4H, $CH_3C\underline{H}_2$–), 3.88, 4.05 (2m, 12H, $CH_3C\underline{H}_2$–Ar), 6.33 (s, 1H, methylene–H), 8.86, 9.71, 9.80, 11.43 (4s, 4H, meso–H). Analysis, Cal: C 77.74, H 8.69, N 8.63. Found: C 77.37, H 8.06, N 8.43. UV-VIS (CH_2Cl_2): 418, 556, 658. Mass: m/e 649,

7. NMR($CDCl_3$): δ –0.52, –1.48 (2s, 2H, NH), 0.6, 0.7 (2t, 6H, $C\underline{H}_3CH_2$–), 1.05 (t, 3H. $C\underline{H}_3CH_2Ar$), 1.3 (m, 1H, $ArC\underline{H}_2CH_3$), 1.8 (m, 15H, $C\underline{H}_3CH_2Ar$), 2.6, 2.7 (2s and 2m at the base, 11H, $(C\underline{H}_3)_2C$ and $CH_3C\underline{H}_2$–), 3.64, 3.8, 3.9, 4.2 (4m, 11H, $CH_3C\underline{H}_2Ar$), 7.2 (s, 1H, H on the exocyclic ring), 8.5, 9.48, 9.5 (3s, 3H, meso–H). UV-VIS(CH_2Cl_2): 434, 536, 694 nm. Mass: m/e 600.

10,11. NMR($CDCl_3$): δ 0.43, 0.6 (2s, 9H, $Si(C\underline{H}_3)_3$), 0.49 (m, 6H, $C\underline{H}_3CH_2$–), 1.78 (m, 18H, $\underline{CH}_3CH_2Ar$), 2.47, 2.55 (2m, 4H, $CH_3C\underline{H}_2$–), 3.81, 3.87, 3.95 (3m, 12H, $CH_3C\underline{H}_2Ar$), 4.05, 4.4 (2s, 3H, $-OCH_3$), 8.66, 8.68, 9.21, 9.29, 9.6, 9,64 (6s, 3H, meso–H). UV-VIS(CH_2Cl_2): 438, 692. Mass: m/e 675.

13. NMR($CDCl_3$): δ -2.1, -1.9 (2s, 2H, NH), 0.9 (m, 6H, $C\underline{H}_3CH_2$-), 1.8 (m, 18H, $C\underline{H}_3CH_2$-), 2.9, 3.14 (2m, 4H, $CH_3C\underline{H}_2$-), 6.94, 8.5 (2bs, 4H, hydrogens on the quinone ring), 8.9,9.56, 9.6, 9.7 (4s, 4H, meso-H). UV-VIS (CH_2Cl_2): 362, 470, 502, 670, 728. ($CHCl_3$): 362, 472, 506, 686, 740. (MeOH): 358, 470, 512, 758. Analysis: Cal. C 80.5, H 7.99, N 8.95. Found: C 80.9, H 8.22, N 8.72. Mass: m/e 627.

14 NMR($CDCl_3$): δ -2.29, -2.15 (2s, 2H, NH), 0.00 (t, 6H, $C\underline{H}_3CH_2$-), 1.7 (m, 18H, $C\underline{H}_3CH_2Ar$), 2.88, 3.3 (2m, 4H, $CH_3C\underline{H}_2$-), 3.51 (s, 6H, $N(C\underline{H}_3)_2$), 3.58, 3.75 (2m, 12H, $CH_3C\underline{H}_2Ar$), 7.36, 8.26 (2d, hydrogens on the six membered ring), 8.75, 8.94, 9.1, 9.3 (4s, 4H, meso-H). UV-VIS (CH_2Cl_2): 481, 530, 857.

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