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VINYL GROUP PROTECTION IN PORPHYRINS AND CHLORINS: ORGANOSELENIUM DERIVATIVES

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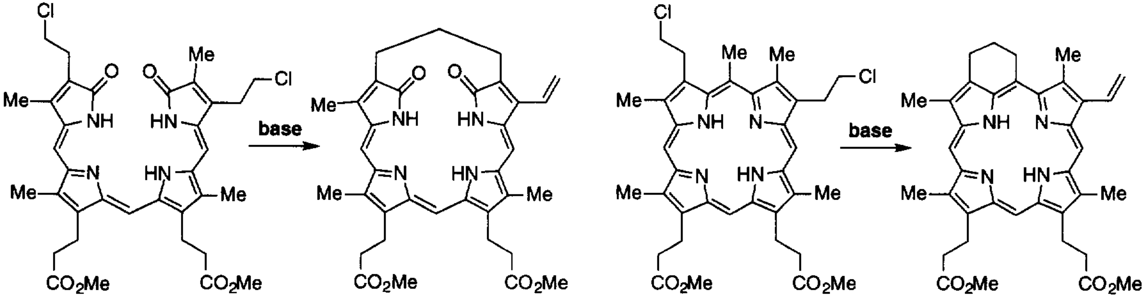
Abstract: The o-nitrophenylselenoethyl functionality is a useful protected vinyl group in porphyrins and chlorins, and its use is demonstrated in the Vilsmeier formylation reaction which has been shown to adversely affect unmodified vinyl groups in tetrapyrrole systems. The X-ray crystal structure for 3-(2-o-nitrophenylselenoethyl)-3-devinylchlorin-e$_6$ trimethyl ester **14** is reported. © 1997, Elsevier Science Ltd. All rights reserved.

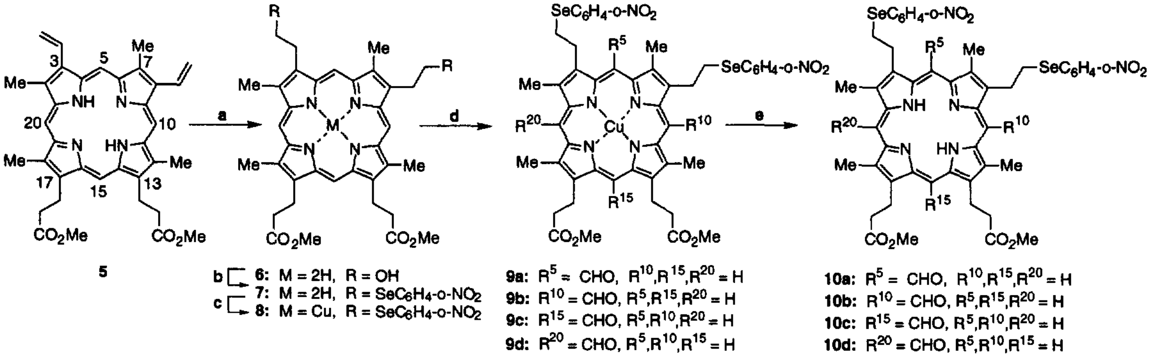
Substituent manipulations of naturally occurring tetrapyrrole derivatives such as those from heme and chlorophyll-a produce a large number of chemically and biologically relevant compounds.[1] Many of these reactions affect the sensitive vinyl functionalities attached to the chromophore, with the result that vinyl protection is required. Vinyl modified groups such as the chloroethyl substituent,[2] while useful, become problematic when alkaline deprotection from base sensitive tetrapyrroles is attempted. For example, attempted base-catalyzed deprotection of bis(2-chloroethyl)biliverdin **1** resulted in dehydrohalogenation *and* cyclization, to form a bridged biliverdin derivative **2**.[3] Basic deprotection of 3-(2-chloroethyl)-3-devinylchlorin-e$_6$ trimethyl ester derivatives also resulted in a mixture of undesired side products,[4] and dehydrohalogenation of, for example, the 5-methyl-3,8-bis(2-chloroethyl)porphyrin **3** led to the formation of the porphyrin **4** bearing a vinyl and a novel six-membered ring.[5] The cyclization reaction presumably occurred by way of a mechanism similar to that proposed for the **1** → **2** transformation. In this paper we focus on vinyl-protection during Vilsmeier meso-formylation of the macrocycle in porphyrins and chlorins; such reactions have been shown [4a,6] to yield acrolein derivatives if the vinyl groups are not protected.

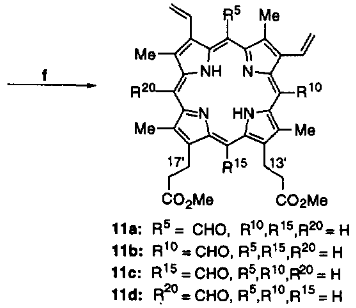


1 **2** **3** **4**

Organoselenium chemistry has been commonly used for conversion of alkyl halides or alcohols into olefins.[7-9] Gossauer's group made use of selenium activation to produce vinyl-substituted bile pigments.[10-13] In our laboratories, we converted propionate side chains into acrylate substituents in porphyrin derivatives,[14] and Jacobi et al. recently used a pyrrole selenide derivative to synthesize a vinyl substitued dipyrromethenone.[15] We now show that the o-nitrophenylselenoethyl substituent is a useful vinyl protected group in porphyrins and chlorins, and that deprotection can easily be accomplished under mild, non-basic conditions.

Our synthetic approach to meso-formylporphyrins **11a-d** (Scheme 1) represents a typical example of the methodology, and Scheme 2 illustrates a new route to 20-formylchlorin-e_6 trimethyl ester[4a] **17**. According to standard protocols,[2] the vinyl groups in protoporphyrin-IX dimethyl ester **5**,[16] were converted into the corresponding hydroxyethyl substituents, giving **6** in 73% yield. Conversion of **6** into the selenium porphyrin **7** using o-nitrophenylselenocyanate and tri(*n*-butyl)posphine in CH_2Cl_2 was accomplished in 80% yield. With the vinyl groups protected for the model Vilsmeier reaction, insertion of copper (to give **8**) followed by formylation using $POCl_3$ and DMF provided the meso-formylporphyrin isomers **9a-d** in 80% yield. Demetallation with 5% H_2SO_4/TFA yielded **10a-d** in 70% yield. Finally, deprotection by oxidation with 30% H_2O_2 in THF to the selenoxide followed by elimination gave the four meso-formylprotoporphyrin-IX dimethyl ester isomers **11a-d** in 67% yield. In the similiar synthesis of chlorin **18**, only one formyl isomer is formed because of enhanced nucleophilicity at the 20 position due to the saturation at ring-D.[17]





Scheme 1: Synthetic route to meso-formylprotoporphyrin-IX dimethyl ester isomers **11a-d**. *Reaction conditions*: **a**: 1. $Tl(NO_3)_3 3H_2O$, $MeOH/CH_2Cl_2$, rt, 30 min. 2. SO_2, HCl, rt, 5 min. 3. Me_3SiI, cyclohexene, $CHCl_3$, rt, 1 h. 4. $NaBH_4$, $MeOH/CH_2Cl_2$, rt, 1 h. **b**: o-nitrophenylselenocyanate, n-Bu_3P, CH_2Cl_2, rt, 4 h. **c**: copper(II) acetylacetonate, $CHCl_3$, reflux, 1 h. **d**: 1. DMF/$POCl_3$, $ClCH_2CH_2Cl$, 80°C, 15 h. 2. sat. $NaHCO_3$, 70°C, 3 h. **e**: 5% H_2SO_4/TFA, rt, 15 min. **f.** 30% H_2O_2, THF/H_2O, rt, 5 h.

Separation of the four isomers **11a-d** using silica gel HPLC (0.5% THF/CH_2Cl_2) indicated a ratio of 5:8:14:72 respectively, and an elution order of **11a**:**11b**:**11d**:**11c**. Regiochemistry of the three isomers **11a,c,d** was determined by analysis of two NOE experiments, involving irradiation of the coinciding 13^1-CH_2 and 17^1-CH_2 signals followed by irradiation of the formyl proton signal (Figure 1). By exclusion, the regiochemistry of **11b** was deduced.

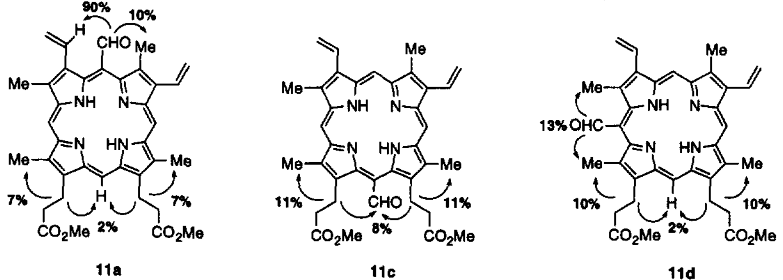
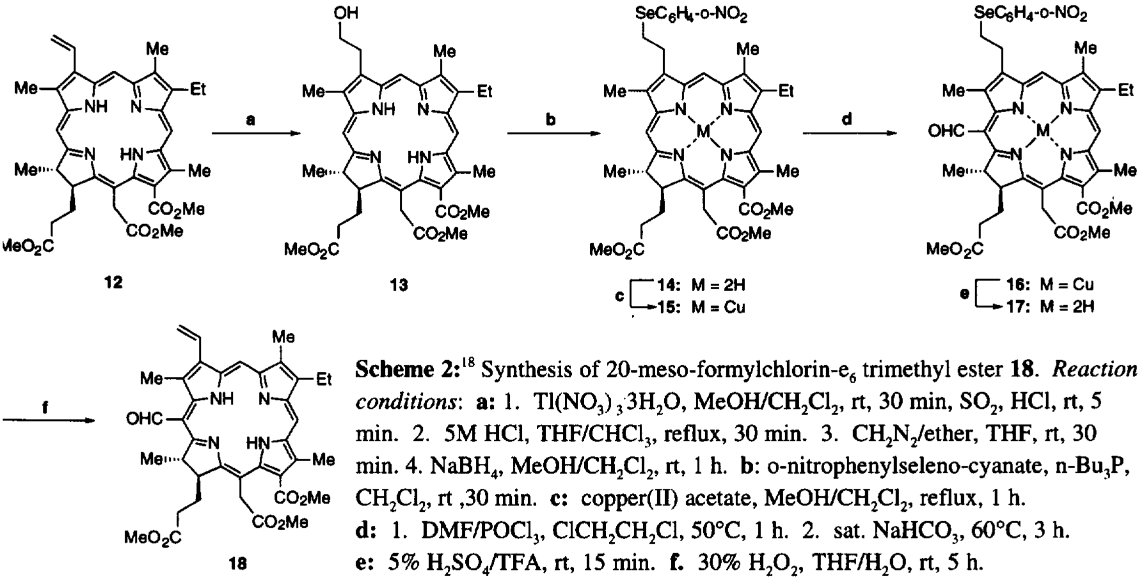


Figure 1: NOE Connectivities for **11a,c,d.**



Scheme 2:[18] Synthesis of 20-meso-formylchlorin-e_6 trimethyl ester **18**. *Reaction conditions*: **a**: 1. $Tl(NO_3)_3{\cdot}3H_2O$, $MeOH/CH_2Cl_2$, rt, 30 min, SO_2, HCl, rt, 5 min. 2. 5M HCl, $THF/CHCl_3$, reflux, 30 min. 3. CH_2N_2/ether, THF, rt, 30 min. 4. $NaBH_4$, $MeOH/CH_2Cl_2$, rt, 1 h. **b**: o-nitrophenylseleno-cyanate, n-Bu_3P, CH_2Cl_2, rt ,30 min. **c**: copper(II) acetate, $MeOH/CH_2Cl_2$, reflux, 1 h. **d**: 1. $DMF/POCl_3$, $ClCH_2CH_2Cl$, 50°C, 1 h. 2. sat. $NaHCO_3$, 60°C, 3 h. **e**: 5% H_2SO_4/TFA, rt, 15 min. **f.** 30% H_2O_2, THF/H_2O, rt, 5 h.

The structure of the chlorin selenide **14** was confirmed by an X-ray crystal structure (Figure 2).[19] The chlorin ore is essentially flat except for the pronounced twist out of the plane shown by the atoms responsible for the chlorin unctionality. Hydrogen atoms of the central core are localized on N(1) of the pyrrole bearing the selenium substituent nd on the opposite pyrrole nitrogen, N(3). The o-nitrophenyl group bonded to Se is coplanar with the core, enabling the nolecules to stack in a head-to-tail fashion along the crystallographic **a** direction.

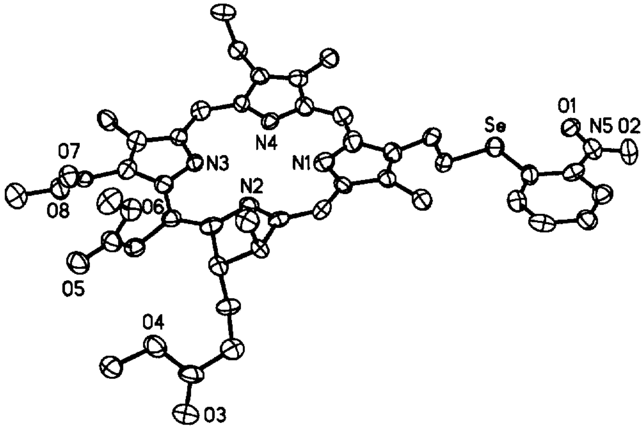


Figure 2: X-ray crystal structure of **14**.

The o-nitrophenylselenoethyl substituent is being further investigated as a vinyl protective group in a multistep ynthesis of 5- and 10-meso-methylprotoporphyrin-IX dimethyl ester isomers, the hemins of which should be useful robes of heme oxygenase mechanism and specificity.[20] Such base sensitive meso-methyl-porphyrins provide another xample (e.g. **3** → **4**) of a situation where selenium chemistry is useful because deprotection of the corresponding (2-hloroethyl)porphyrin derivatives leads to unexpected cyclization products.

Acknowledgements: This work was supported by grants from the National Institutes of Health (HL 22252) and the National Science Foundation (CHE-96-23117).

References and Notes:

1. K. M. Smith and J. A. S. Cavaleiro, *Heterocycles* **1987**, *26*, 1947.
2. G. W. Kenner, S. W. McCombie and K. M. Smith, *Liebigs Ann. Chem.* **1973**, 1329.
3. E. D. Sturrock, J. R. Bull, R. E. Kirsch, R. K. Pandey, M. O. Senge and K. M. Smith, *J. Chem. Soc., Chem. Commun.* **1993**, 872.
4. (a) K. M. Smith, G. M. F. Bisset and M. J. Bushell, *J. Org. Chem.*, **1980**, *45*, 2218. (b) B. Gerlach, S. E. Brantley and K. M. Smith, manuscript in preparation.
5. I. Meunier (UC Davis), unpublished results.
6. A. W. Nichol, *J. Chem. Soc. (C)* **1970**, 903.
7. K. B. Sharpless, M. W. Young and R. F. Lauer, *Tetrahedron Lett.* **1973**, 1979.
8. K. B. Sharpless and M. W. Young, *J. Org. Chem.* **1975**, *40*, 947.
9. P. A. Grieco and J. Y. Jaw, *J. Org. Chem.* **1981**, *46*, 1215.
10. A. Gossauer and J. -P. Weller, *Chem. Ber.* **1978**, *111*, 486.
11. A. Gossauer and J. -P. Weller, *J. Am. Chem. Soc.* **1978**, *100*, 5928.
12. J. -P. Weller and A. Gossauer, *Chem. Ber.* **1980**, *113*, 1603.
13. A. Gossauer, F. Nydegger, E. Benedikt and H. -P. Kost, *Helv. Chim. Acta* **1989**, *72*, 518.
14. K. M. Smith, M. Miura and I. K. Morris, *J. Org. Chem.* **1986**, *51*, 4660.
15. P. A. Jacobi, G. Jiasheng, S. I. Hauck and S. H. Leung, *Tetrahedron Lett.* **1996**, *37*, 6069.
16. M. Grinstein, *J. Biol. Chem.* **1947**, *167*, 515.
17. R. B. Woodward and V. Skaric, *J. Am. Chem. Soc.* **1961**, *83*, 4676.
18. Chlorin-e_6 trimethyl ester **12** is readily available from chlorophyll-a: see ref. 4, and K. M. Smith, D. A. Goff and D. J. Simpson, *J. Am. Chem. Soc.* **1985**, *107*, 4946.
19. *Crystal Data.*: $C_{43}H_{47}N_5O_8Se$, **14**, M = 840.82, orthorhombic, a = 7.607(4), b = 14.671(11), c = 34.61(3) Å, U = 3863(5) Å^3 (by least-squares refinement on diffractometer angles for 46 centered reflections), λ = 1.54178 Å, space group $P2_12_12_1$; Z = 4, D_c = 1.446 g cm^{-3}, $F(000)$ = 1752; green plates; crystal dimensions 0.004 x 0.12 x 0.50 mm, $\mu CuK\alpha$ = 1.83 mm^{-1}, Siemens P4 diffractometer and Cu rotating anode operating at 15 kW; scan type 2Θ-Θ, T = 130(2) K, $2\Theta_{max}$ = 112.3°; 2981 data, 2914 unique, R(int) = 0.025; 1824 > 2σ(I), XABS2 absorption correction, solution and refinement using Siemens SHELXTL v. 5, refinement based on F^2, wR (all data) = 0.1252, R (obsd data) = 0.0696, hydrogens bonded to nitrogen located on difference map, remaining hydrogens added geometrically; all hydrogens refined using riding model; largest peak in final difference Fourier map = 0.35 eÅ^{-3}; absolute structure parameter (Flack) -0.02(7). Tables of atom positions, thermal parameters, and a complete listing of bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre.
20. J. Torpey, D. A. Lee, K. M. Smith and P. R. Ortiz de Montellano, *J. Am. Chem. Soc.* **1996**, *118*, 9172.

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