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SYNTHESIS OF NUCLEOSIDE ADDUCTS OF PORPHYRINS AND CHLOROPHYLL DERIVATIVES

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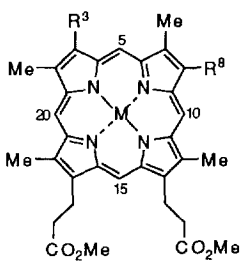
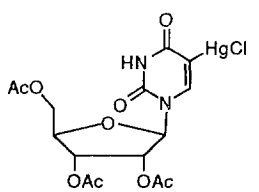
Abstract: Treatment of various vinyl-porphyrins and -chlorins with 2',3',5'-tri-*O*-acetyl-5-chloromercuriuridine under "Heck conditions" affords both *trans*- and *gem*-nucleoside adducts in ratios which depend upon the nature of the vinyl-porphyrin or -chlorin.

In recent years, porphyrins coupled with nucleoside bases have attracted great attention due to their strong tumoricidal activity against human maligant melanoma,[1] and as antiviral agents for the purification of blood contaminated with HIV-1.[2] Recently, using comparative molecular field analysis, a series of porphyrins were screened by Debnath et al.[3] for anti-HIV-1 activity, and the preliminary results were quite promising. It has been shown[e.g.4] that porphyrin derivatives covalently bonded to nucleoside bases may be important as synthetic DNA intercalating agents. Sessler and coworkers[5a] have reported some interesting synthetic bisporphyrin cytosine-guanine base pairs, and sapphyrin-cytosine conjugates[5b] that act as selective through-membrane carriers for mononucleotides (e.g. guanosine-5'-monophosphate) at neutral pH. Thus, there appears to be a growing interest in syntheses of porphyrin-based nucleoside adducts due to their potential biological and pharmaceutical importance.

A number of years ago we reported the synthesis of a series of substituted porphyrins with unsaturated side chains by using palladium(II) catalyzed carbon-carbon coupling methodology (the Heck reaction),[6-8] and this novel reaction gave *trans*- alkene products in excellent yield. In addition to porphyrins, we reported that chlorins can also be converted into the corresponding styrene derivatives upon treatment with phenylmercuric chloride. We now report an extension of this methodology to the preparation of nucleoside conjugates.



1 M = Zn; $R^3 = R^8 = CH{=}CH_2$
3 M = Zn; $R^3 = CH{=}CH_2$; $R^8 = H$
4 M = 2H; $R^3 = R^8 = H$



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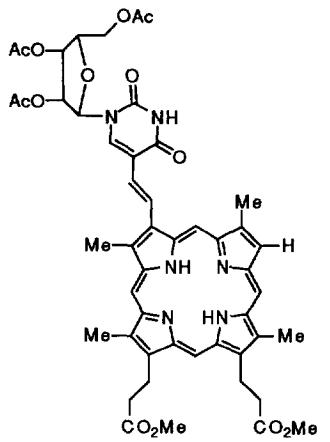
Reaction of zinc(II) protoporphyrin IX dimethyl ester **1** (in which vinyl groups are present at the 3- and 8-positions; IUPAC nomenclature), with 2',3',5'-tri-*O*-acetyl-5-chloromercuriuridine **2** gave a mixture of products. In order to limit the formation of mixtures, the monovinylporphyrin, zinc(II) 3-vinyldeuteroporphyrin IX dimethyl ester **3**

(prepared from deuteroporphyrin IX dimethyl ester **4**), was used as the substrate. Reaction of **2** with **3** under Heck reaction conditions[7] gave two major products in a combined yield of 36%. After removal of zinc, these products were separated into individual isomers by preparative chromatography. From the proton NMR data, the more polar band was identified as the *trans*- isomer **5** [Figure 1A; CH=CHUridine, δ 8.99, 7.37 (each d, J 16.3 Hz)] whereas the faster moving band was characterized as the *gem*-isomer **6** [Figure 1B; H_aH_bC=C(Uridine)Porphyrin, δ 7.52, 6.12 (each d, J 1.34 Hz)].



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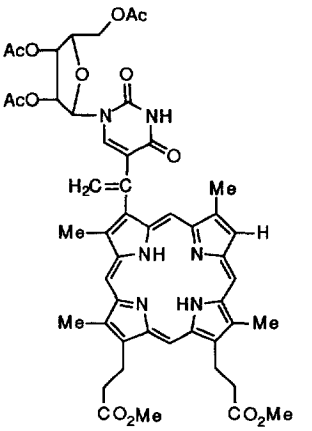

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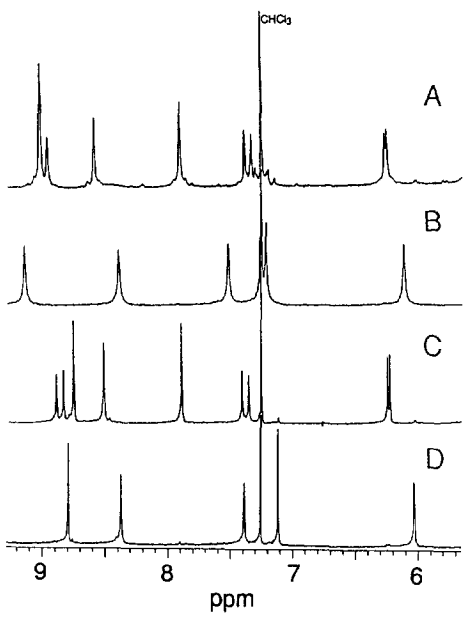


Figure 1: Vinyl region in the proton NMR spectra (300 MHz, in $CDCl_3$) A, *trans*- uridinylporphyrin **5**; B, *gem*-uridinylporphyrin **6**; C, *trans*- uridinylchlorin **8**; and D, *gem*-uridinylchlorin **9**

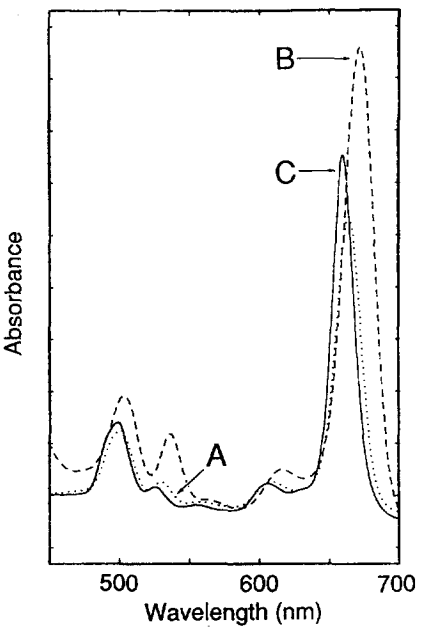
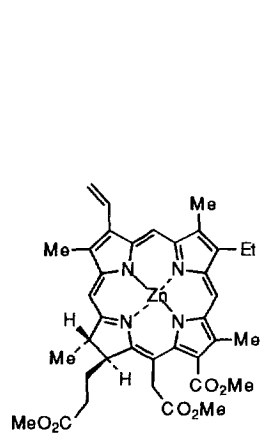


Figure 2: Optical spectra, in CH_2Cl_2, of A, chlorin-e_6 trimethyl ester (····); B, adduct **8** (- - -); and C, adduct **9** (——).

These results were surprising, because under similar reaction conditions, when vinylchlorins and vinylporphyrins were reacted with a series of mercurated analogues, the isolated products had only the *trans*- alkene configuration. In

order to explore the versatility of this reaction, several chlorins (17,18-dihydroporphyrins) were used as substrates. Thus, zinc(II) chlorin e_6 trimethyl ester **7** gave two isomers **8** and **9** in the ratio of 2.2 : 1. Figure 1 shows the diagnostic regions in the proton NMR spectra. *trans*-Compound **8** (Figure 1C) clearly shows the CH=CHUridine protons at δ 8.87 and 7.38, respectively, with a coupling constant of 16.4 Hz; the *gem*-isomer **9** displayed (Figure 1D) the H_aH_bC=C(Uridine)Chlorin resonances at δ 7.38 and 6.02 (J 1.6 Hz). The electronic absorption spectra of the chlorin e_6 related conjugates (**7-9**) are shown in Figure 2.

By comparison with the starting material **7** (664 nm), and *gem*- isomer **9** (660 nm), the long wavelength absorption for *trans*- isomer **8** was observed at 672 nm, due to extension of the conjugation in the chromophore. Using similar chemistry, zinc(II) methyl pyropheophorbide-a **10**, produced the isomer **11** (after removal of zinc), with only a trace of the *gem*-isomer **12**, whereas zinc(II) methyl 9-deoxypyropheophorbide-a **13**, produced both the *trans*-isomer **14** and the *gem*-compound **15** in approximately equal amounts; clearly, the ratio of the isomers produced is dependent upon the nature of the tetrapyrrole substrate.[9]



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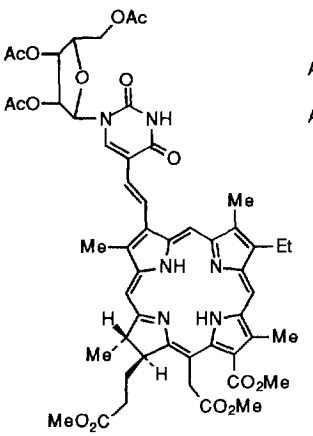

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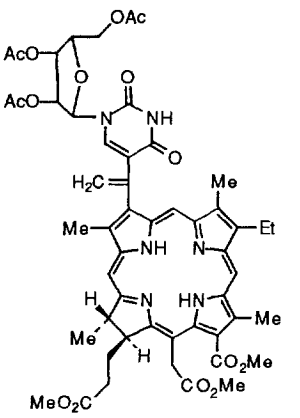

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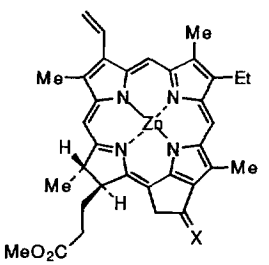
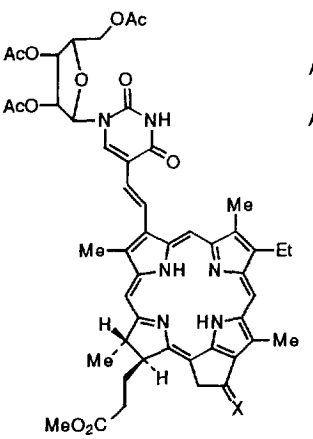
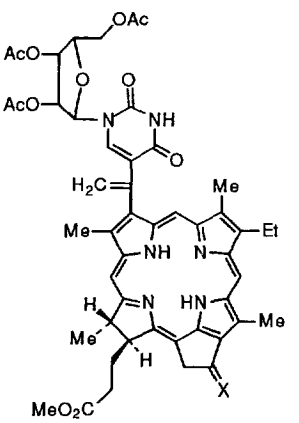


10 X = O
13 X = H_2



11 X = O
14 X = H_2



12 X = O
15 X = H_2

The effects of electronic and steric factors in the olefin arylation and carboalkoxylation reaction with organopalladium compounds (terminal and internal additions) have been studied in depth by Heck et al.[7]

This methodology is currently being explored for the condensation of other long wavelength tetrapyrrole systems (such as bacteriochlorins and purpurins) with a variety of nucleosides and analogues. Due to their long wavelength absorptions, and ability to intercalate with DNA, these novel compounds might be useful candidates for the treatment of cancer by photodynamic therapy, and for the inactivation of viruses in blood components. The compounds reported herein are currently being evaluated for biological activity.

All new compounds were characterized by proton NMR, elemental analysis, and/or high resolution mass spectroscopy.

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9. A typical procedure for the preparation of these compounds is as follows: To vinyl-porphyrin or -chlorin (0.12 mmol), and 2',3',5'-tri-*O*-acetyl-5-chloromercuriuridine (**2**) (0.36 mmol) in dry dimethylformamide (5 mL) and acetonitrile (2 mL) was added $LiPdCl_3$ solution [prepared by refluxing LiCl (0.72 mmol) and $PdCl_2$ (0.36 mmol) in acetonitrile (5 mL) for 1h under nitrogen] dropwise at room temperature. The reaction mixture was kept at 35 to 40°C and progress was monitored by TLC. The mixture was then filtered through a bed of Celite to remove Pd^0. After the usual work up, the product was purified by column chromatography (silica gel), eluting with 1.5% methanol in dichloromethane. The two isomers (*trans-* and *gem-*) were separated, and were obtained in combined yields of 35-40%. The ratio of the isomers varied with the substrates.

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