Alkylation of β-(Hydroxymethyl)pyrroles: A New Synthesis of Porphobilinogen and Other Trisubstituted Pyrroles for Photodynamic Therapy

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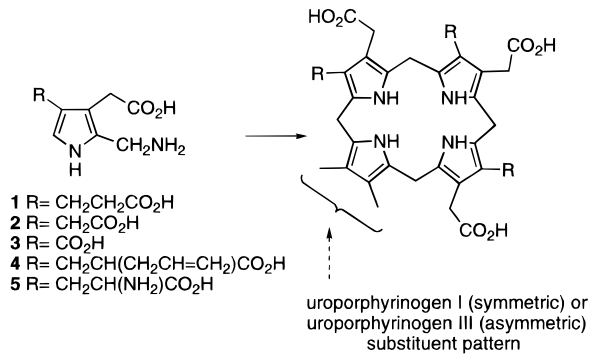
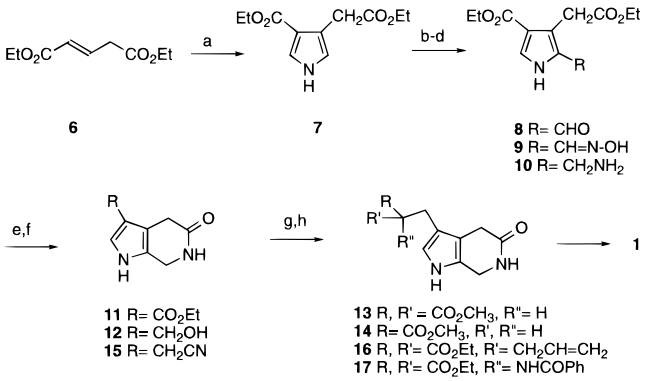
The trisubstituted pyrrole porphobilinogen (PBG; **1** in Scheme 1) is a key intermediate in the biosynthesis of porphyrins and corrins and the central building block for the biosynthesis of hemoglobin, chlorophyll, and many other brightly-colored pigments of life.[1] First isolated[2] and assigned its structure 40 years ago,[3,4] PBG has remained a popular synthetic target. Successful total syntheses have been reported from substituted pyrroles,[5] from pyrrole itself,[6] and from azaindole.[7] Yet despite its deceptively simple-looking achiral structure, PBG remains difficult to synthesize in preparatively useful amounts and expensive to buy (>$10 000 per gram).[8]

Interest in a practical and efficient route to PBG that could furnish analogs and congeners has been fueled by the emergence of photodynamic therapy (PDT) using synthetic, porphyrin-based pigments to treat systemic cancers, superficial malignancies, and small, localized tumors.[9] PDT relies on the administration of chromophores that sensitize cells to irradiation with visible or near-visible light to generate singlet oxygen. Appropriate sensitizers must show selectivity for the malignant tissue and must be cleared promptly in order to achieve timely treatment regimens. In a major advance, oral administration of 5-aminolevulinic acid, the biosynthetic precursor of PBG, was shown to sensitize tumor cells to light for only a few hours.[10] Since 2-(aminomethyl)pyrroles like **1** can self-assemble nonenzymatically into uroporphinoids quite readily under neutral[11] or acidic[3] conditions, we reasoned that PBG and suitable analogs might be transformed into porphyrin or corrin-like pigments, either *in vivo* or *in vitro*, for PDT.

Scheme 1



Scheme 2[a]



[a] Key: (a) TsCH(Li)N=C; (b) $POCl_3$, DMF; (c) NH_2OH−EtOH; (d) H_2, $Pd(OH)_2$, HCl, EtOH; (e) NaOEt−EtOH; (f) DIBAL−THF, rt; (g) dimethyl malonate (5 equiv), NaH (5 equiv), 24 h; (h) NaCN (1.5 equiv), DMF, cat. H_2O, 130−140 °C, 24 h.

To implement the first stage of that strategy, we report a short, high-yielding synthesis of PBG itself and of several related 2-(aminomethyl)pyrroles. Key features of our approach include (1) an adaptation of the van Leusen pyrrole construction to the acidic electrophile, diethyl glutaconate, (2) a highly regioselective aminomethylation of the product pyrroloacetic ester, and (3) a new method for the direct alkylation of 3-(hydroxymethyl)pyrroles that accommodates a variety of simple carbon nucleophiles such as malonates, substituted malonates, acetoacetates, and cyanide. Of special interest is the capability of installing acetate, propionate, or larger side chains at the 3-position of the pyrrole nucleus leading to PBG analogs and homologs **2**−**5**.

Simple enones and enoates react with the sodium salt of tosylmethyl isocyanide (TosMIC) to afford 3- or 3,4-disubstituted pyrroles.[12] Under those conditions, however, diethyl glutaconate (**6**) (Scheme 2) underwent deprotonation and self-condensed to form a dimeric tetraester as the exclusive product. To minimize proton transfer and retard dimerization, **6** (1 equiv) was added to the lithium salt of TosMIC [1 equiv, THF, −70 °C, generated using $LiN(TMS)_2$] with slow warming to rt. In that fashion, multigram quantities of pyrrole diester **7** could be obtained in 70−80% yield. Formylation of **7** under Vilsmeier−Haack conditions gave the expected aldehyde **8** as the predominant product (8:1 ratio, 96% overall) that, without separation, was converted to the

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oxime **9** and hydrogenated over $Pd(OH)_2$. Upon basic workup, the desired amino diester **10** cyclized to lactam **11**, which was easily obtained pure by chromatography in 83% overall yield from **8**.

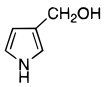
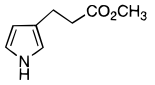
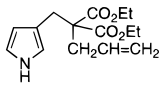
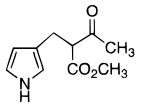
Selective reduction of **11** with DIBAL under controlled conditions furnished (hydroxymethyl)pyrrololactam **12** (86%), a key intermediate in our synthesis. We envisioned that substitution of the OH group in **12** with appropriate carbon nucleophiles might proceed without activation as an acetate or tosylate by a process of elimination−addition involving a β-alkylidenepyrrolenine cation.[13] In fact, when **12** was heated with the sodium salt of dimethyl malonate (5 equiv, DMF, 130 °C, 4 h), diester **13** was obtained in 65% yield. Nucleophilic deesterification and decarboxylation (1.3 equiv NaCN−DMF, 140 °C, 63%) furnished the methyl ester of PBG lactam **14**, a common intermediate in virtually all previous syntheses of **1**. The present synthesis gives **14**, which can be saponified to **1**, in seven steps and 20% overall yield, representing a short and efficient route from commercially available reactants.

The direct alkylation of β-(hydroxymethyl)pyrroles is unprecedented, and several examples of the process (shown in the Table 1) illustrate its scope and generality.[14] Besides undergoing a two-carbon chain extension with dimethyl malonate, compound **12** reacts with NaCN to afford **15**, thus achieving a one-carbon homologation leading to nor-PBG **2**. Substituted malonates such as diethyl allylmalonate or diethyl benzamidomalonate also react with **12** to generate **16** and **17**, respectively, indicating the success of the method in forming quaternary carbon centers. Similar alkylations on the parent system, 3-(hydroxymethyl)pyrrole **18**, also give the expected products.

Pyrroles **16** and **17** represent clinically promising new directions for synthetic PBG analogs, both in PDT and other medical applications. Hydrolysis and decarboxylation of **16** afford allylated PBG **4**, which may find use in assembling haptens for the preparation of more avid anti-PBG antibodies. Such immunoreagents are currently employed to monitor serum PBG levels,[15] which are good indicators of lead poisoning in children.[16]

The synthesis of **17** illustrates an approach to new pyrrole-containing α-amino acids like **5** of therapeutic interest in PDT. Since sophisticated active transport mechanisms for α-amino acids have evolved in eucaryotic cells,[17] compounds like **17** may serve as precursors for highly tissue-selective PDT sensitizers, the attendant advantages of which include lower toxicity and reduced skin photosensitization.

Table 1. Nucleophilic Alkylations of β-(Hydroxymethyl)pyrroles

Reactant	Nucleophile[a]	Product (Yield)
12	$NaCH(CO_2CH_3)_2$	**13** (68%)
12	NaCN[b]	**15** (35%)
12	$KC(CH_2CH{=}CH_2)(CO_2Et)_2$	**16** (66%)
12	$NaC(NHCOPh)(CO_2Et)_2$	**17** (44%)
 **18**	$NaCH(CO_2CH_3)_2$	 **19** (53%)[c]
18	$NaC(CH_2CH{=}CH_2)(CO_2Et)_2$	 **20** (70%)
18	$CH_3COCH(Na)CO_2Et$	 **21** (66%)
18	NaCN	 **22** (52%)

[a] Representative conditions: 5 equiv of nucleophile, DMF, 130−140 °C, 4 h. [b] 10 equiv used. [c] Combined yield for alkylation and deesterification−decarboxylation.

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Supporting Information Available: Full experimental procedures as well as spectral and physical data are given for all new compounds reported (8 pages).

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