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Photoactivated enediynes: targeted chimeras which undergo photo-Bergman cyclization

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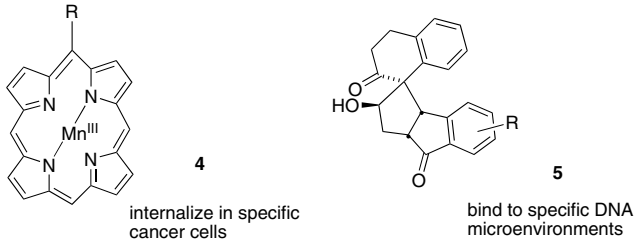
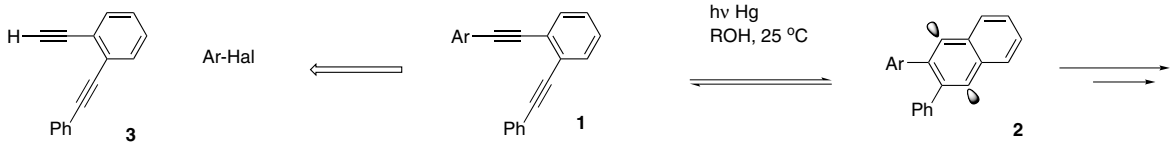
Abstract—Chimeric enediynes composed of a photoactivatable warhead coupled either to a porphyrin or spiroalcohol have been prepared. The molecules underwent photoactivation to produce diaryl radicals paving the way for applications in targeted photodynamic therapy.

1. Introduction

Among the emerging modalities for the treatment of various cancers, photodynamic therapy [PDT] has received considerable attention in recent years.[1] In principle, this modality would permit systemic administration of a photoactivated prodrug, which is then transformed into a cytotoxin on exposure to light from a tunable laser. Numerous systems have been investigated including photosensitizing dyes, including some with the propensity to selectively accumulate in neoplastic tissue.[2] Our interest in this field stems from the finding that the photo-Bergman cycloaromatization of aryl enediynes can be induced on exposure to UV light,[3] and the subsequent aryl radicals have the ability to degrade either nuclear[4] or cellular macromolecules[5] depending on structure.[6] Given the simplicity of the process and the synthetic availability of aryl enediynes,[3–6] we became interested in the assembly of enediyne chimeras, where a targeting moiety might enhance selective uptake of the



prodrug. Our goal was to produce substrates **1** as prodrugs for diyls **2**, using transition mediated coupling of readily available enediyne core **3** (Scheme 1). Having previously applied this methodology to the preparation of protein-degrading conjugates,[7] we were particularly interested in (i) a chimera with the potential for cellular uptake and (ii) a chimera with the potential to effect selective binding to specific nucleic acid sequences. After surveying various options, we elected to assemble



Scheme 1. Synthetic accessibility and utility of photo-Bergman chimeras.

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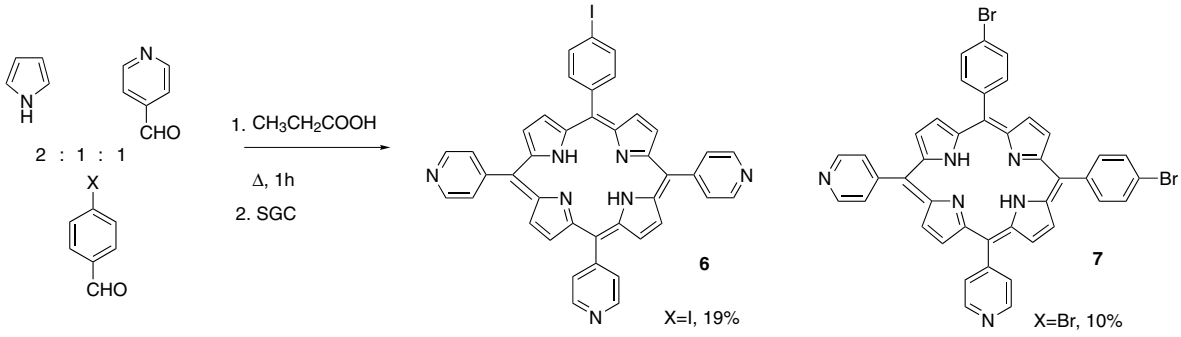
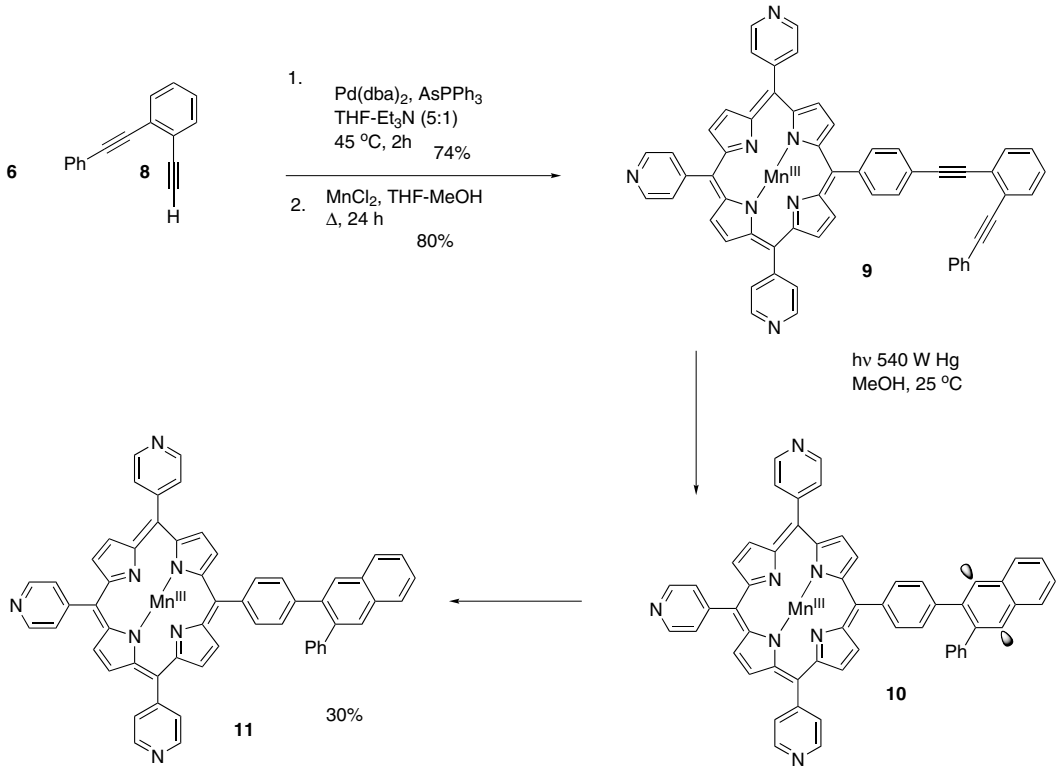
porphyrin enediynes **4** and spiroalcohol enediyne conjugates **5**, respectively (R = enediyne).

2. Porphyrin enediyne chimeras

Porphyrins have played a key role in the development of photodynamic therapy with one of the best known phototoxins, Photofrin® showing promising clinical activity for the PDT treatment of specific cancers.[8] The mechanism of phototoxicity induced by porphyrins involves generation, through a metalloporphyrin intermediate, of singlet oxygen. Though an enediyne-porphyrin chimera would afford analysis of the interplay of oxygen radicals with carbon based radicals, another benefit lies in targeted delivery. It has been demonstrated that specific porphyrins have the ability to accumulate in rapidly proliferating cells (e.g., tumor cells) with a degree of selectivity, suggesting enediyne-porphyrin chimeras to be attractive targets.[9] Mindful of the reactivity of porphyrin templates, we wished to demonstrate a simple and effective route to enediyne chimeras via a versatile halogenated template. The most direct route was a classic three-component coupling of appropriate haloaryl carboxaldehydes, giving access to either monoiodo substrate **6** or dibromo substrate **7** in moderate yield (Scheme 2).[10] With reactive substrate **6** in hand, direct coupling of pre-assembled enediyne **8** was effected using Pd methodology.[7] The resulting chimera was converted to the corresponding metalloporphyrin **9** following overnight reflux (Scheme 3). Though under these conditions, the linear enediyne was stable, on irradiation, smooth conversion to the cycloaromatized arene **11** was effected, presumably via diyl radical **10** or its counterpart. With

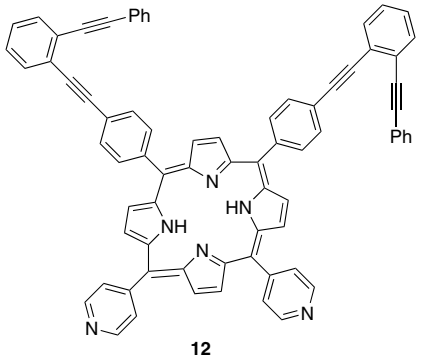


Scheme 2. One pot synthesis of haloaryl pyridyl porphyrin templates.



Scheme 3. Preparation and photo-Bergman cyclization of porphyrin–enediyne chimera.

the photo-Bergman cyclization demonstrated, we also wished to provide proof of principle for the production of a bis-enediyne chimera. Dibromoporphyrin **7** underwent analogous coupling to yield adduct **12** in moderate (60%) yield, and the photocyclization gave the bis-arene albeit in lesser yield (~20%).



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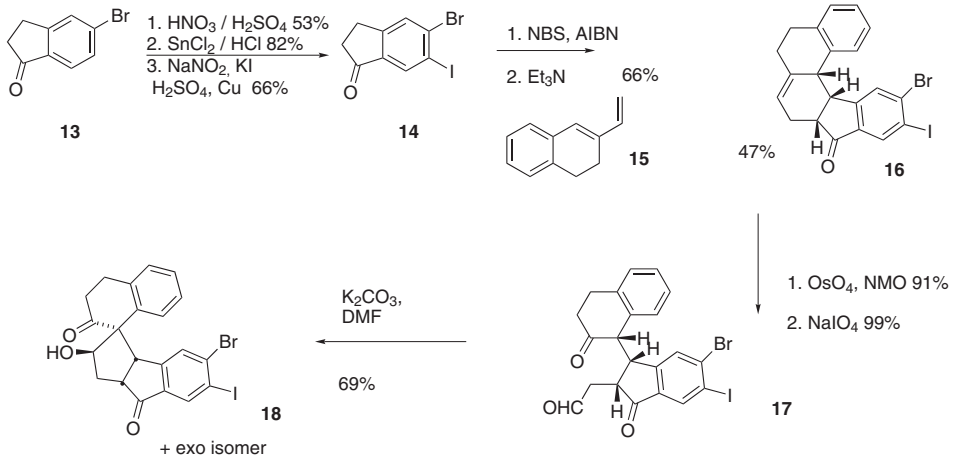
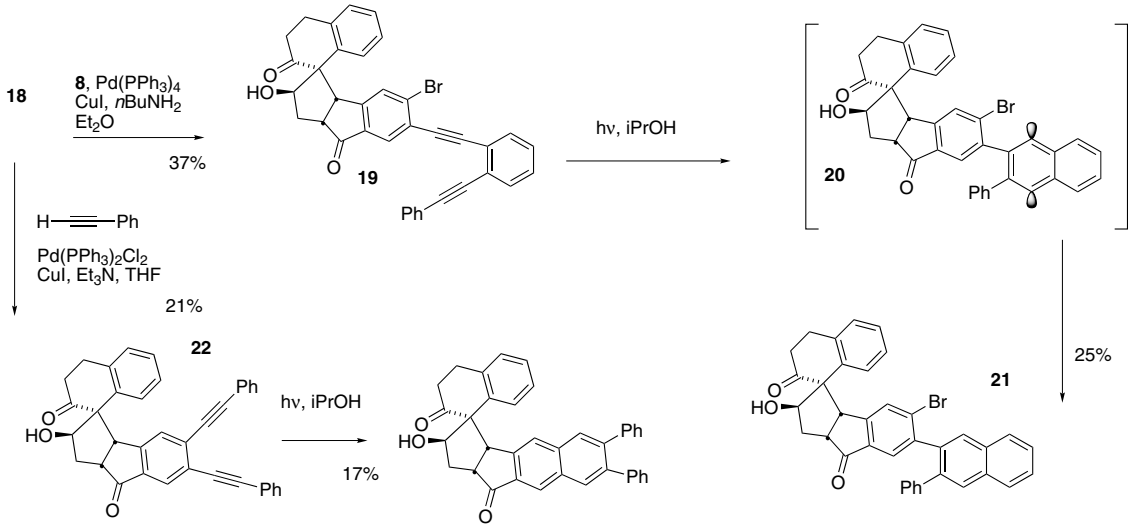
3. Spiroalcohol enediyne chimeras

Bulged microenvironments in both RNA and DNA are of general biological significance, implicated as intermediates in frame-shift mutagenesis, imperfect homologous recombination, as binding motifs for regulatory proteins involved with viral replication, and in the etiology of a number of human neurodegenerative genetic diseases.[11] Compounds capable of binding to bulged nucleic acid targets could have significant therapeutic potential. Though success has been hindered by lack of an available substrate, which can recognize bulged sites in preference to conventional duplexes, the Goldberg and Jones laboratories recently reported a series of spiroalcohols **5**, which have up to nM affinity for specific bulges.[12] The synthetic route to this unusual class exploits an intramolecular aldol reaction as a key step, and we became interested in modification to produce an enediyne chimera. Given the impact of structure on affinity for nucleic acid sequences, we wished to demonstrate access to a broad class, and elected to produce a mixed



13 **14** **15** **16** **17** **18**

Scheme 4. Preparation of haloaryl spirocyclic bulge-binder template.



Scheme 5. Photo-Bergman cyclization of bulge-binder enediyne chimeras.

halogenated template for this purpose. Commencing with bromoindanone **13**, an *ortho*-iodo was installed, prior to induction of an in situ Diels–Alder with diene **15** (Scheme 4). Adduct **16** was converted to keto aldehyde **17** via classical oxidative cleavage, and the key spiroaldolization reaction proceeded as anticipated to give **18** easily separable from its *exo* counterpart. With the template in hand, selective coupling with enediyne **8** was effected, and the substrate **19** underwent smooth photoconversion to the corresponding arene **21** (Scheme 5). Underscoring the flexibility of **18**, sequential coupling with phenyl acetylene was also demonstrated, the product **22** likewise undergoing photoconversion to the corresponding arene. In both cases the material balance is starting material, suggesting that further improvements in photoconversion efficiency might be attainable. In summary, efficient synthesis of enediyne porphyrin and enediyne spiroalcohol chimeras have been effected. The products, as expected, underwent smooth photoactivation. Biological studies involving cellular uptake and selective incapacitation of macromolecules will now be undertaken, to advance these potential candidates as PDT agents.

Acknowledgements

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