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Photoassisted Synthesis of Enantiopure Alkaloid Mimics Possessing Unprecedented Polyheterocyclic Cores

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Supporting Information

ABSTRACT: Enantiopure alkaloid mimics are synthesized via high yielding intramolecular cycloadditions of photogenerated azaxylylenes tethered to pyrroles, with further growth of molecular complexity via post-photochemical transformations of primary photoproducts. This expeditious access to structurally unprecedented polyheterocyclic cores is being developed in the context of diversity-oriented synthesis, as the modular design allows for rapid "pre-assembly" of diverse photoprecursors from simple building blocks/diversity inputs.

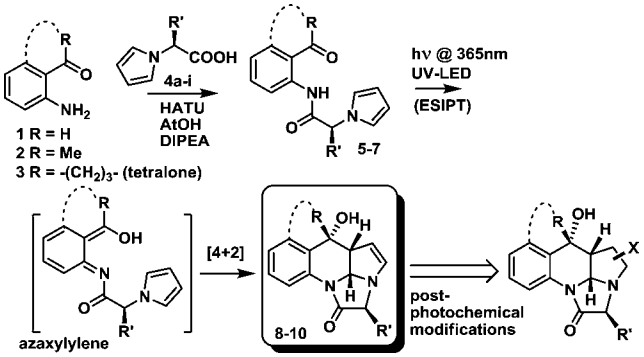
High throughput synthetic methods are blamed for "steering discovery efforts toward achiral, aromatic compounds" while natural products, possessing a broad spectrum of bioactivity, look nothing like the sp^2-dominated aromatic heterocycles in the proverbial "flatland" of the lead discovery. Lovering[1] has shown convincingly that as drug candidates progress through the stages of development their average saturation factor fsp3[2] grows steadily, starting from fsp3 = 0.36 for the "discovery" stage, and increasing for compounds which cleared Phase I through Phase III clinical trials (0.38 → 0.43 → 0.45). An average fsp3 for a sample of 1179 *approved drugs* is 0.47. It appears that no one deems these findings controversial. However, the practical difficulties of synthesizing complex, sp^3-rich natural products drive the observed *shift into the flatland*, where the well-developed catalytic sp^2−sp^2 coupling reactions dominate.

Our approach to this problem, in the context of diversity-oriented synthesis, is the modular "assembly" of photoprecursors with subsequent intramolecular photoinduced cyclizations as the key step delivering a rapid increase in complexity while also increasing saturation and installing additional stereogenic centers. The synthesis of photoprecursors, which by design are largely unsaturated, is based on well-developed coupling reactions, fully compatible with high throughput combinatorial synthetic techniques.

The time-proven hetero Diels−Alder reactions are a powerful example of synthesis of partially saturated heterocyclic scaffolds.[3] However, the scope of these ground state reactions is limited, and the search for new cycloadditions is well-justified and ongoing. We have recently discovered one of such reactions which has a tremendous synthetic potential. We found that azaxylylenes, photogenerated via the excited state intramolecular proton transfer (ESIPT) in aromatic *o*-amidoketones, could be trapped intramolecularly by tethered unsaturated pendants.[4]

In this Communication, we report that the *N-tethered* pyrroles undergo an exclusive [4 + 2] cycloaddition to photogenerated azaxylylenes yielding polycyclic aminals **8**−**10** which possess a reactive enamine moiety suitable for subsequent transformations. Chiral *α*-substituted *N*-pyrrole acetic acids **4** are readily available on the multigram scale from *α*-amino acids.[5] They are readily coupled with the photoactive moiety, aromatic amino-aldehydes and ketones **1**−**3**, and irradiated as shown in Scheme 1 to yield bowl-shaped tetracyclic *enantiopure* aminals **8**−**10** with the high *exo*-R and *endo*-OH diastereoselectivity.

Scheme 1



Aminals **8**−**10** and the products of their postphotochemical transformations are structurally related to the alkaloids of the chaetominine[6] and kapakahine[7] families, except that in a pseudo symmetric fashion, the benzene ring is "translocated" from the five-membered pyrrole- to the six-membered piperidine moiety, resulting in a new and unique polyheterocyclic core which has not been previously reported. Chaetominine (Figure 1), which is isolated from Chaetomium species of endophytic fungi, is active against two lines of human cancer cell lines (SW1116, 28 nM; and K562, 21 nM), which triggered synthesis efforts in several groups, starting with Snider's total synthesis in 2007.[6b]

The novel *N*,*N*-ethanone-linked pyrrolo[2,3-*b*]quinoline core in photoproducts **8**−**10** has a reactive enamine moiety, which makes them excellent synthons for subsequent modifications to further increase molecular complexity. Scheme 2 illustrates the rapid "pre-assembly" of photoprecursor **7b** from aminotetralone **3** and alanine-derived pyrrole **4b** and its photoinduced

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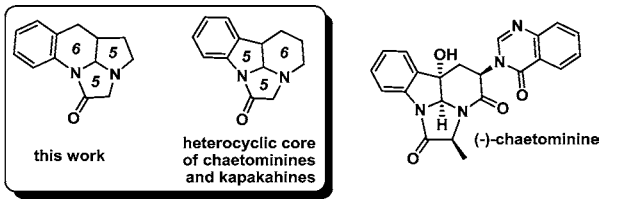
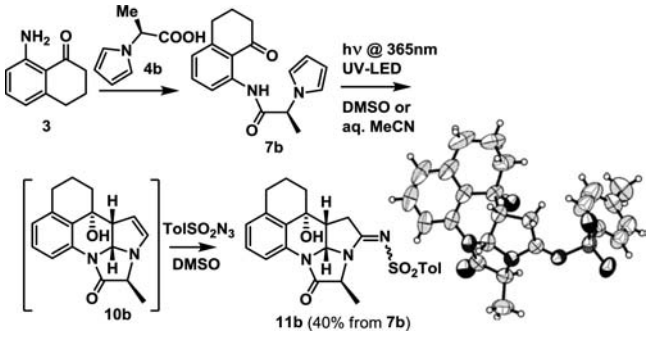


Figure 1. Pyrido[2,3-*b*]indole core of chaetominines and kapakahines and the pyrrolo[2,3-*b*]quinoline core accessed in this work.

Scheme 2



conversion to pentacyclic enamine **10b**. Without additional purification, **10b** is reacted with toluenesulfonyl azide yielding cyclic *N*-sulfonyl amidine **11b** (the ORTEP drawing of its X-ray structure is shown).[8]

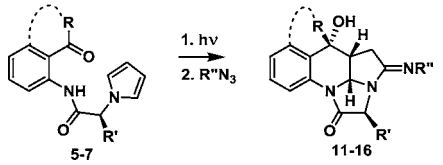
Initially, 5% aqueous acetonitrile was used for the irradiation step, after which the solution was preconcentrated, diluted with DMSO, and reacted with the azide. Quantitative conversion of primary photoproducts, enamines **8**−**10** to amidines **11**−**16** occurs in DMSO at ambient temperature within 2 h. Table 1 summarizes the overall two-step photoassisted conversion of precursors **5**−**7** to *N*-sulfonyl cyclic amidines **11**−**16**, attesting to the broad scope of this synthetic sequence.

Later it was found that the irradiation step can also be carried out in DMSO, so that photoprecursor **7b** is converted to amidine **11b** in a two-step, one-pot fashion. Furthermore, sulfonyl azides do not absorb much above 350 nm, so they are not considerably affected by the UV-LED@365nm irradiation. This allows implementing an even simpler one-pot procedure, where **7b** is irradiated in DMSO *in the presence of tosyl azide*, which is added to the solution before irradiation. Figure 2 shows the condition optimization runs and reveals that while a two-step, one-pot procedure in DMSO is slightly superior (84% *over two steps*), the one-step procedure is still reasonably competitive: the best yield is 71%. It also reveals that, although the azide step is bimolecular, overconcentration does not help the yield, which at 1 M is only 38%.

DMSO is an atypical choice for photochemical reactions. However, due to its hydrogen bonding ability, it is known to stabilize the ESIPT species[9] extending the excited state lifetimes and therefore enhancing the reactivity of photogenerated azaxylylenes.

Only in the case of aminobenzaldehyde-based photoprecursor **5h**, both diastereomers of the final amidine, *syn*, 43% (OH and the amidine cycle are on the same face of the quinoline moiety) and *anti*, 29%, are isolated. The rationale for this decrease in stereospecificity is that the small formyl group in the aldehyde photoprecursor is more freely rotatable than in ketones.

Table 1. Two-Step Photoassisted Conversion of Precursors 5−7 to Cyclic *N*-Sulfonyl Amidines 11−16



R' [aa of origin]	R"	Product [a]	Yield [b]
R=Me (aminoacetophenone-based)			
6a H [**4a** GLY-based]	Ts	**13a** (A)[c]	35%
6b Me [**4b** ALA]	Ts	**13b** (A)	57%
6c iPr [**4c** VAL]	Ts	**13c** (A)	69%
6d [**4d** MET]	Ts	**13d** (A)	56%
6e [**4e** ORN]	Ts	**13e** (B)	36%
6f [**4f** LYS]	Ts	**13f** (B)	37%
6g Ph [**4g** D-PHGLY]	Ts	**13g** (A)[c]	77%
6h Bn [**4h** PHE]	Ts	**13h** (A)[c]	84%
6h Bn [**4h** PHE]	SO_2PhCl	**14** (A)[c]	80%
6h Bn [**4h** PHE]	$PhCO_2Me$	**15** (A)	68%
6h Bn [**4h** PHE]	SO_2thienyl	**16** (A)	73%
R=H (aminobenzaldehyde-based)			
5h Bn [**4h** PHE]	Ts	**12h** (A)[c]	72%[d]
5g Ph [**4g** D-PHGLY]	Ts	**12g** (B)[c]	51%
R = -(CH$_2$)$_3$- (aminotetralone-based)			
7b Me [**4b** ALA]	Ts	**11b** (A)[c]	40%
7f  [**4f** LYS]	Ts	**11f** (B)[c]	24%

[a]Product obtained with procedure: (**A**) one pot, irradiated and reacted with the azide in DMSO; (**B**) irradiated in aq MeCN, concentrated, diluted with DMSO, reacted with the azide. [b]Isolated yield over two steps. [c]X-ray structure is available. [d]43% *syn*- and 29% *anti*-.

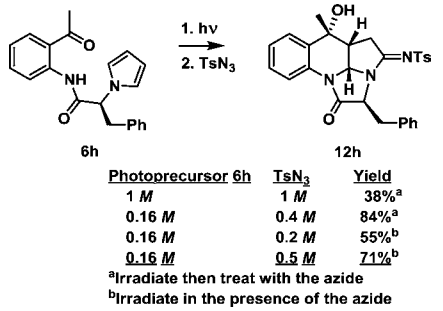


Figure 2. One-step vs two-step procedure in DMSO.

Irradiation of **6h** in DMSO with subsequent addition of dimethyl acetylene dicarboxylate (DMAD) at an elevated temperature (80 °C) yields **17h** as a result of [2 + 2] cycloaddition to enamine **9h** (Ssheme 3). At higher temperatures, azepino-[2,3-*b*]-quinolinol **18h** is obtained, presumably via electrocyclic ring-opening in **17h**.

In the presence of acids, the enamine moiety in the primary photoproducts **8**−**10** expectedly forms iminium ions, which can be trapped by a variety of nucleophiles. Given that there are a number of natural and non-natural amino acids possessing a secondary (ω)-nucleophilic functionality, this offers an opportunity to trap these iminium ions intramolecularly. We found not only that such trapping is possible but also that in

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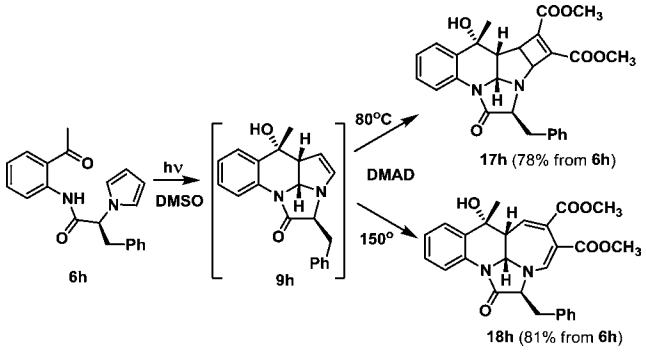
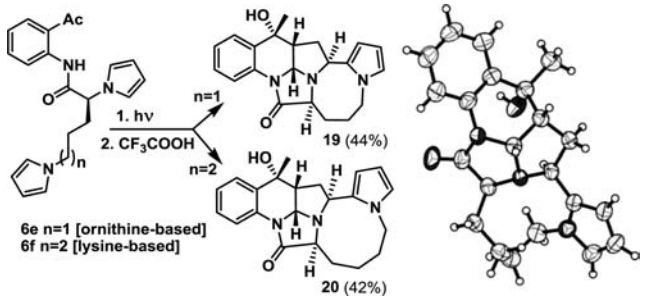
Scheme 3



this sequence of post-photochemical modifications a new C−C bond can be formed. In bis-pyrrole substituted carboxylic acids **4e** and **4f**, which are readily obtained from bis-amino acids ornithine and lysine, the generated iminium ions are capable of aromatic electrophilic substitution in the second pyrrole moiety, leading to the formation of large eight-membered *diazocane*- and nine-membered *diazonane* rings in moderate yields, Scheme 4 (the ORTEP drawing of the X-ray structure of 1,4-diazonane **20** is shown).

Scheme 4

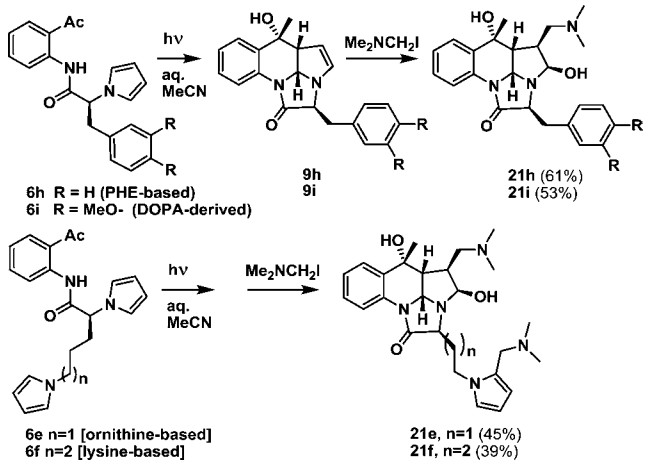


Having employed C-nucleophiles for trapping of the iminium cations, we also looked into C-electrophiles for their generation, as enamines are well-known to react with soft carbon electrophiles. Utilization of C-electrophiles, such as Eschenmoser's aminomethylating reagent, allows for an additional diversity input connected to the polyheterocyclic scaffold via a carbon−carbon bond. As shown in Scheme 5, the one-pot procedure is run in 5% aqueous acetonitrile, which stabilizes the primary photoproduct, enamine **9**. After irradiation excess water is removed by adding anhydrous sodium sulfate, and Echenmoser's salt is added to yield hemi-aminals **21**. In the case ornithine- and lysine-based photoprecursors **6e** and **6f**, the terminal pyrrol moiety reacts with excess Eschenmoser's reagent yielding diamines **21e** and **21f**.

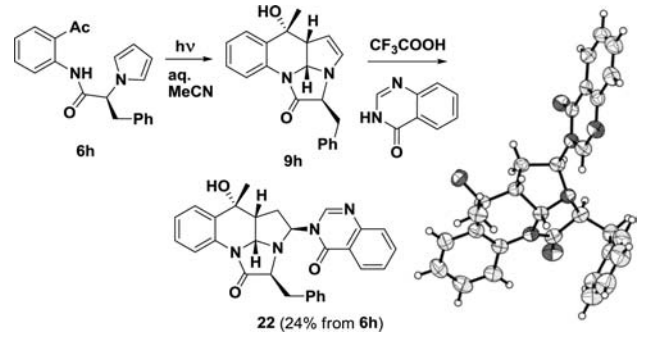
Unlike the protic acid-induced reaction shown in Scheme 4, the bulky Eschenmoser electrophile prevents intramolecular cyclization involving terminal pyrroles in **9f,e**. Our attempts to force the cyclization in diamines **21e,f** by treating them with trifluoroacetic acid failed. Judging by NMR, they instead eliminate water from the pyrrolidine ring to form enamines.

The cyclic iminium ion, generated from the primary photoproducts, enamines **8**−**10**, with a protic acid is capable of trapping more complex external nucleophiles as additional diversity inputs. Scheme 6 illustrates such intermolecular

Scheme 5



Scheme 6



trapping by quinazolone in a reaction with phenylalanine-based **9h**.

In summary, the new intramolecular cyclization of photogenerated azaxylylenes with tethered pyrrole pendants based on α-amino acids provides a powerful tool for building complex enantiopure alkaloid mimics possessing unique polyheterocyclic cores, with multiple (5−6) stereogenic centers, structurally similar to the chaetominine and kapakahine families of alkaloids. The photoprecursors for these compounds are readily synthesized via 2−3 simple and well-developed steps. The key photochemical step allows for a dramatic growth of molecular complexity augmented with experimentally simple post-photochemical steps. The resulting enantiopure polyheterocyclic scaffolds are rich in sp^3 carbons (fsp3 ≈ 0.3−0.6) and possess multiple new stereogenic centers, including quaternary.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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