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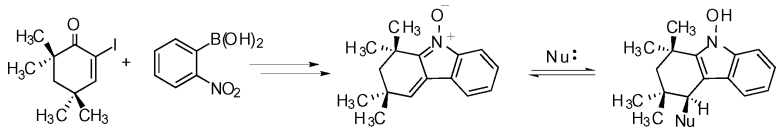

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Identification of a Novel Michael Acceptor Group for the Reversible Addition of Oxygen- and Sulfur-Based Nucleophiles. Synthesis and Reactivity of the 3-Alkylidene-3*H*-indole 1-Oxide Function of Avrainvillamide

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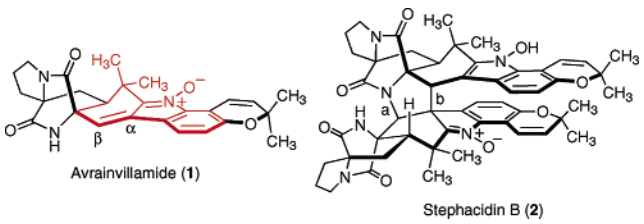
Functional groups that bond covalently to active-site nucleophiles frequently form the basis for the design of potent and selective enzyme inhibitors, and those that form covalent bonds reversibly (e.g., carbonyl groups, boronic esters) can be especially valuable in pharmaceutical development.[1] In studies directed toward the synthesis of the alkaloids avrainvillamide (**1**) and stephacidin B (**2**), we have identified the 3-alkylidene-3*H*-indole 1-oxide group as a new function that is capable of reversible covalent bond formation with heteroatom-based nucleophiles.

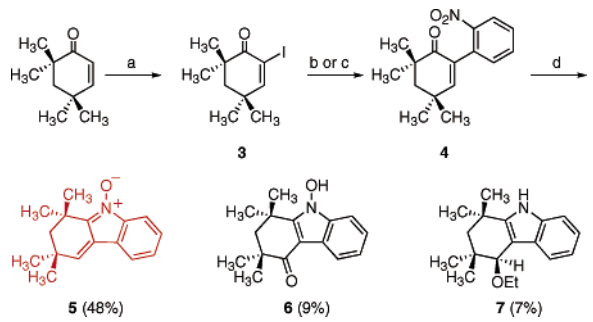


Avrainvillamide and stephacidin B, formally a dimer of **1** (vide infra), have been separately identified in culture media from various strains of *Aspergillus*. Both compounds exhibit antiproliferative activity, and **1** is reported to exhibit antimicrobial activity against multidrug-resistant bacteria.[2] Avrainvillamide is apparently the first natural product with a 3-alkylidene-3*H*-indole 1-oxide function; our synthetic efforts were therefore initially directed toward the development of a viable strategy to introduce this group. A process that forms the nitrogen heterocycle with C−C bond formation between carbon 3 (α in structure **1**) and the arene ring was recognized to be especially convergent in the context of targets **1** and **2**. A two-step organometallic coupling−reductive condensation sequence was envisioned (Scheme 1).[3]

To implement the proposed two-step process, the model substrate **3** was prepared by iodination[4] of 4,4,6,6-tetramethylcyclohex-2-en-1-one[5] (96%, Scheme 1). A Suzuki coupling of **3** with 2-nitrophenylboronic acid then afforded the α-arylated ketone **4** in 73% yield (Scheme 1).[6] Alternatively, **4** could be formed from **3** in 70% yield by using 2-iodonitrobenzene as the coupling partner in the presence of $Pd_2(dba)_3$ and copper powder.[7] Reductive condensation of **4** was accomplished in the presence of activated zinc powder,[8] providing the 3-alkylidene-3*H*-indole 1-oxide **5** in 48% yield, as well as the (separable) byproducts **6** (9%) and **7** (7%). Spectroscopic data supported the assignment of the major product as **5**; this assignment was confirmed by single-crystal X-ray analysis (Figure 1).

Deuterium-labeling experiments (see Supporting Information) established that product **5** had been formed with the expected connectivity, that is, with nitrogen bonding to the carbonyl carbon (this was also shown for **4** → **7**), but, interestingly, in the formation of the *N*-hydroxy indole byproduct **6**, nitrogen was shown to bond to the *β*-carbon of enone **4** (potentially a 5-endo-trig closure).

Scheme 1[a]



[a] Reaction conditions: (a) I_2 (3 equiv), DMAP (0.2 equiv), CCl_4−pyridine, 49 °C, 96%. (b) $Pd_2(dba)_3$ (0.05 equiv), 2-nitrophenylboronic acid (1 equiv), 2-(di-*t*-butylphosphino)biphenyl (0.20 equiv), $Ba(OH)_2 \cdot 8H_2O$ (3.0 equiv), THF−H_2O, 38 °C, 73%. (c) 2-iodonitrobenzene (2 equiv), $Pd_2(dba)_3$ (0.025 equiv), Cu (powder, 5 equiv), DMSO, 70 °C, 70%. (d) Zn (dust, 2.7 equiv), 1 M NH_4Cl (2.2 equiv), EtOH, 48 °C, 64%.

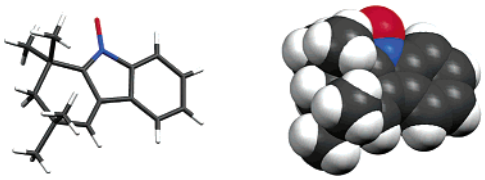


Figure 1. Capped-stick and space-filling models of **5** from X-ray data.

Control experiments demonstrated that the (unstable) byproduct **7** was formed slowly from **5** under the reaction conditions; however, the yield was low (10%), and paths connecting **4** and **7** not involving **5** are readily envisioned. In practice, byproducts **6** and **7** were minor, and **5** was easily purified chromatographically.

Solutions of **5** in benzene or chloroform were found to be quite stable when protected from light (vide infra); however, in methanol a surprisingly facile, reversible 1,5-addition of solvent to the α,*β*-unsaturated nitrone group occurred (eq 1).[9] At 23 °C in pure methanol-d_4, the half-life for the conversion of **5** to **8** (Nu = OCD_3) was approximately 5 h. The equilibrium between **5** and **8** was significantly temperature dependent. At equilibrium, the ratio of **8** (Nu = OCD_3) to **5** was 2:1 at 23 °C and 10:1 at −20 °C (7 days to achieve). Warming a cold (−20 °C) solution of **8** and **5** at equilibrium quickly reestablished equilibrium at the higher temperature (23 °C), now from the product side (**8** → **5**). Removal of methanol in vacuo led to complete and clean reversal of adduct formation (**8** → **5**). Addition of methanol to **5** was found to be catalyzed by both base ($NaOCH_3$, 10 mol %, equilibrium <10 min, 23 °C) and acid (CH_3CCO_2H, 10 mol %, $t_{1/2} \approx 1$ h, 23 °C; Cl_3CCO_2H, 10 mol %, equilibrium < 10 min, 23 °C). As expected, small amounts (≤10 mol %) of catalyst did not perturb the

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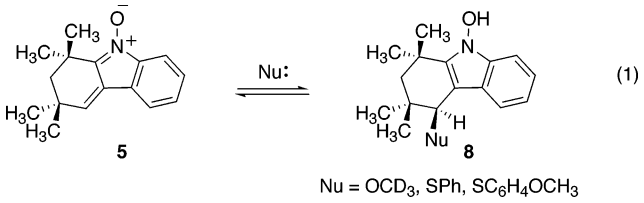
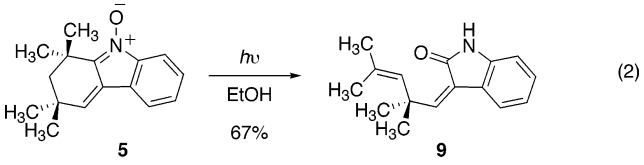
equilibrium between **5** and **8**; however, stoichiometric quantities of sodium methoxide did (**8**:**5** = 100:1 at equilibrium, 10 equiv of $NaOCH_3$).



(1)

Thiols were also found to add cleanly and reversibly to **5** in the presence of a base, but not without. For example, addition of 4-methoxybenzenethiol (1.2 equiv) to **5** in the presence of triethylamine-d_{15} (0.2 equiv) in CD_2Cl_2 at 23 °C afforded the 1,5-adduct (**8**, Nu = $SC_6H_4OCH_3$) quickly (<15 min) and quantitatively (^{1}H NMR analysis). Under similar conditions, addition of thiophenol (**8**, Nu = SC_6H_5) proceeded to afford a 9:1 ratio of adduct to starting material, whereas the ratio was >98:2 at −40 °C (^{1}H NMR analysis, $k_{8\rightarrow5}$ = 0.25 ± 0.15 s^{-1} M^{-1} at −40 °C).[10] Neither addition was significantly affected by the presence (or absence) of oxygen. The 1,5-adducts were highly labile toward silica gel, to the extent that they could not be purified chromatographically without inducing complete reversal (**8** → **5**).

Other transformations of **5** of note include its reduction with $NaBH_4$ in methanol (**8**, Nu = H, 89%) and its photochemical rearrangement under ambient light or, more rapidly, upon direct irradiation (200 W Hg lamp) to form the lactam **9** (eq 2, 67%).[11] The latter transformation may involve an intermediate oxaziridine, as is frequently proposed in the photochemistry of nitrones.[12]



(2)

In contrast to the facile addition of oxygen- and sulfur-based nucleophiles that was observed, all potential nitrogen-based nucleophiles examined to date (e.g., *n*-propylamine, formamide, 2-pyrrolidinone, 2-hydroxypyridine, 2-trimethylsilyloxypyrroline) have failed to produce detectable levels of adducts in reactions with **5**. Given the steric hindrance about the β-position of **5** (see Figure 1), it is remarkable that any nucleophilic addition occurs at all. The failure of amides to add to **5** is of interest given the proposed dimerization of **1** to form **2**; however, the differences between our model system and **1** caution against overinterpretation of this result. In particular, analysis of X-ray data for **2** suggests that there is a stabilizing hydrogen bond between the secondary lactam NH group and the carbonyl oxygen of the adjacent amide; this would be replaced by a repulsive interaction with a methyl group in our model system. Dimerization of **1** to form **2** has been proposed to involve initial formation of bond b in structure **2** and not bond a (as results here might imply, see also ref 2d); however, it should be emphasized that the transformation of **1** to **2** has not yet been demonstrated to occur at all.[2c]

In an effort to explore the potentially greater generality of nucleophilic additions to α,β-unsaturated nitrones, the nitrones derived from the condensation of *N*-phenylhydroxylamine with (*E*)-cinnamaldehyde[13] and (*E*)-4,4-dimethyl-2-pentenal were prepared and subjected to conditions leading to adduct formation with **5** described above. However, in neither case was nucleophilic addition observed. By and large, the acyclic α,β-unsaturated nitrones were found to be unreactive. These observations might point toward the importance of the formation of the aromatic indole structure in **5** → **8**, a driving force that would be lacking in acyclic α,β-unsaturated nitrones. Thus far, our studies have identified the 3-alkylidene-3*H*-indole 1-oxide group as both necessary and sufficient to function as a novel Michael acceptor group for oxygen- and sulfur-based nucleophiles. There is as yet no evidence that this reactivity plays any role in the biological activity of **1** (or **2**), although our findings are certainly intriguing in this regard.

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Supporting Information Available: Experimental procedures for the preparation of all new compounds, tabulated spectral data, and X-ray data of **5** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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