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Efficient Access to the Core of the *Strychnos*, *Aspidosperma* and *Iboga* Alkaloids. A Short Synthesis of Norfluorocurarine

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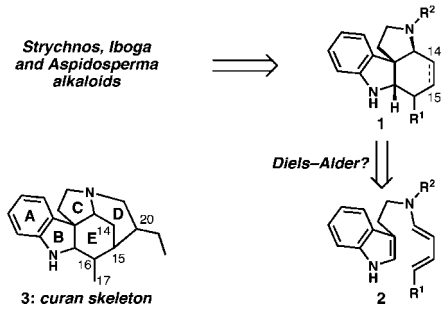
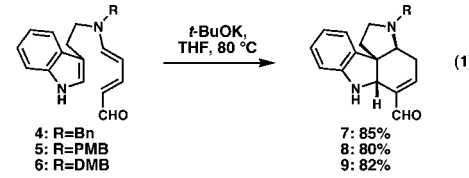
Tetracyle **1** is embedded in many indole monoterpene alkaloids, including those of the *Strychnos*, *Aspidosperma*, and *Iboga* families;[1] for example, it constitutes the ABCE ring system of the curan skeleton (**3**) common to most *Strychnos* alkaloids. Obscured by the lack of unsaturation at the C14−C15 bond of these alkaloids is the possibility of a direct synthesis of this important core structure via an intramolecular Diels−Alder reaction of a tryptamine-derived aminodiene such as **2** (Scheme 1). Such an approach is confronted by two major challenges: (1) indoles are notoriously poor dienophilic components for [4 + 2] cycloadditions; (2) most aminodienes are electron-rich and would be poorly reactive toward the electron-rich indole.[2] For an approach of this type, an ideal strategy avoids indole protection and places an electron-deficient C-atom at R^1 to allow for straightforward elaboration toward natural product targets (see below). A tryptamine-derived Zincke aldehyde (5-amino-2,4-pentadienal, **2**: $R^1 = CHO$)[3,4] fulfills these criteria. A cycloaddition of this special diene with the indole double bond would generate a versatile intermediate for the synthesis of many different indole monoterpene alkaloids; this attractive idea was the inspiration for our group's investigations of Zincke aldehydes, a useful group of conjugated dienes that derive from the ring opening of pyridinium salts.[5] Here, we describe a formal cycloaddition that leads to tetracycles related to **1** and a concise synthesis of the *Strychnos* alkaloid norfluorocurarine.

Inspired by the potential of the prospective cycloaddition, model Zincke aldehyde **4** was synthesized by a pyridinium salt ring opening reaction with N_b-benzyltryptamine.[6] A range of conditions was screened to effect either a concerted cycloaddition or a stepwise bicyclization reaction. Heating **4** at high temperatures (*ca.* 160 °C) led to the discovery of the thermal Zincke aldehyde rearrangement to afford *Z*-α,*β*,*γ*,*δ*-unsaturated amides, as previously reported by our group.[5b,7,8] A variety of Lewis acids and protic acids were unsuccessful in promoting the desired cycloaddition[9] and, in many cases, resulted in indole degradation or apparent Pictet−Spengler-like reactivity. Although attenuation of the nucleophilicity of the indole might have alleviated these problems, we focused on utilizing the unprotected indole to minimize unnecessary manipulations.

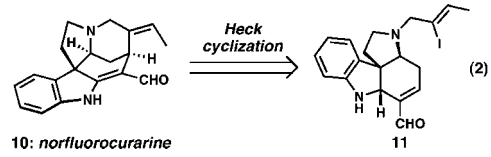
Scheme 1. Intramolecular Cycloaddition Strategy for the Synthesis of Indole Monoterpene Alkaloids, and the Curan Skeleton of Many *Strychnos* Alkaloids





(1)

Ultimately, it was the inherent reactivity of the unprotected indole that enabled the success of the desired reaction. Treatment of **4** with *t*-BuOK in THF at 80 °C in a sealed tube afforded tetracycle **7** in 85% yield (eq 1) via presumed anionic bicyclization;[10−12] as anticipated, the basic conditions had caused conjugation of the alkene with the aldehyde. This key reaction has precedent in the studies of Markó,[10] who showed that related bicyclizations of indole anions can generate the core of the manzamines as well as the indole alkaloids. Our approach distinguishes itself by direct incorporation of a C17 aldehyde, which is a consequence of the use of Zincke aldehyde starting materials, and is particularly enabling for the synthesis of *Strychnos* alkaloids (see below). Zincke aldehydes **5** and **6** afforded tetracyclic products **8** and **9** in similar yields. The relative configuration of the products was assigned by nOe correlations[6] and matched that of the ABCE ring systems of most indole monoterpene alkaloids; the key tetracyclic core of these alkaloids was accessed in just three steps from tryptamine and pyridine.



(2)

With the success of our new stereoselective bicyclization reaction, we turned our attention to the synthesis of the *Strychnos* alkaloid norfluorocurarine (**10**, eq 2).[13,14] We envisioned that an intramolecular Heck reaction[15] of vinyl iodide **11**, inspired by the work of Rawal,[16,17] would serve as the final key step to close the D ring and generate the vinylogous formamide present in **10**. Although the synthesis of **11** was initially pursued by deprotection of **7**−**9** and alkylation, our attempts to remove the benzyl groups by a variety of means were unsuccessful.[18]

The synthesis of **11** begins with known vinylsilane **12** (Scheme 2), which is readily available in one step from 1-(trimethylsilyl)-propyne.[19] Conversion to the allylic bromide allowed for allylation of tryptamine to afford **13**. Ring opening of pyridinium salt **14** with 2 equiv of **13**[20] afforded Zincke aldehyde **15**. Following our optimized procedure for anionic bicyclization, **15** was converted to crystalline tetracycle **16** in 84% yield; the relative stereochemistry was secured by X-ray crystallography. At this stage, an iododesilylation reaction was required to provide Heck substrate **11**;[21]

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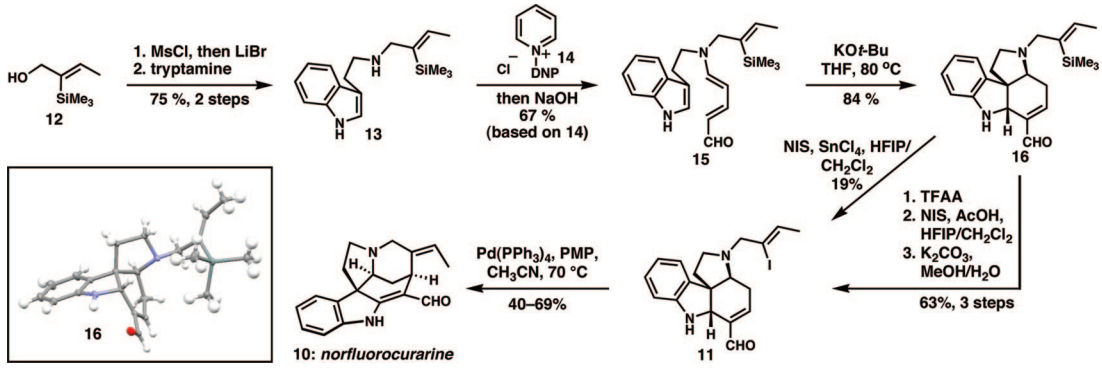
Scheme 2. Synthesis of Norfluorocurarine and X-ray Crystal Structure of Tetracyclic Intermediate **16**



however, the basic tertiary amine and electron-rich aromatic ring led to complex reaction mixtures in which only small quantities of desired vinyl iodide could be observed. Optimization attempts led to the isolation of **11** in 19% yield by direct iododesilylation of **16**; a three-step protocol involving temporary *N*-trifluoroacetylation of the indoline generated **11** in a more reasonable 63% overall yield.[22] Finally, Heck cyclization provided (±)-norfluorocurarine, whose spectral data were in agreement with those previously reported.[13c] The successful route proceeds in five steps from tryptamine or seven steps from 1-(trimethysilyl)propyne using the direct iodination protocol (seven and nine steps, respectively, using the three-step iodination sequence), and its brevity is a consequence of the Zincke aldehyde formal cycloaddition reaction.

We have developed a base-mediated anionic bicyclization reaction of tryptamine-derived Zincke aldehydes to form the ABCE core of many indole monoterpene alkaloids in three steps from tryptamine. Cyclization products are isolated as single diastereomers in high yields. Heck cyclization onto the unsaturated aldehyde generated in the bicyclization reaction afforded the *Strychnos* alkaloid norfluorocurarine. This rapid entry into the *Strychnos* alkaloids paves the way for the synthesis of the more complex members of this family, including strychnine and brucine. Finally, the formal cycloaddition of Zincke aldehydes with a pendant indole-derived metalloenamine suggests the possibility of a general bicyclization reaction of tethered (nonindolic) metalloenamines or enolates to access a variety of complex architectures for alkaloid synthesis. Work along these lines and mechanistic studies are ongoing in our laboratory.

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Supporting Information Available: Complete experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Efforts to carry a vinyl halide substituent through the base-mediated bicyclization reaction led to decomposition, presumably via dehydrohalogenation pathways. A product tentatively assigned as the corresponding alkyne was observed; other products might derive from dehydrohalogenation to afford an unstable allenamine, which could decompose further.

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