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A Biomimetic Approach to the *Strychnos* Alkaloids. A Novel, Concise Synthesis of (±)-Akuammicine and a Route to (±)-Strychnine

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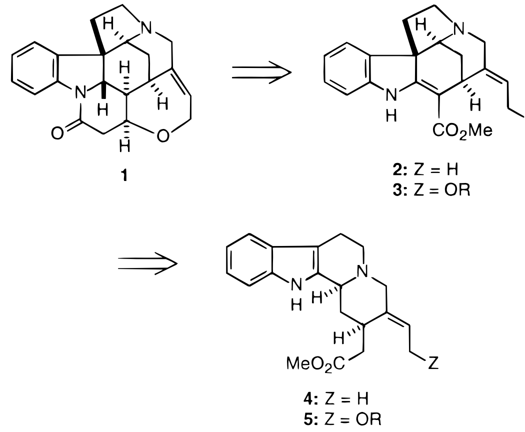
Strychnine (**1**)[1] and akuammicine (**2**)[2] are representative members of the *Strychnos* family of indole alkaloids and have been targets of synthetic investigations since the elucidation of their structures nearly 50 years ago.[3−9] The total synthesis of **1** by Woodward more than 40 years ago arguably marked the genesis of modern synthetic organic chemistry.[4] Today, the Woodward approach still exemplifies how ingenuity and careful planning may be exploited in the design of short and efficient syntheses of complex targets. With the exception of protecting groups, *each* carbon atom introduced into an intermediate was retained in the final product, therefore, the strategy represents the first example of atom economy in organic synthesis.[10] Subsequent to the seminal achievement of Woodward, strychnine did not succumb again to total synthesis until 1992 with the elegant syntheses by Magnus,[5] Stork,[6] Overman,[7] Kuehne,[8] and Rawal.[9] Three total syntheses of akuammicine (**2**) have been recorded by Overman,[11] Kuehne,[12] and Bonjoch and Bosch.[13] Herein we report the implementation of a novel biomimetic strategy to a facile total synthesis of akuammicine (**2**) and an oxygenated analogue that is a potential intermediate in a formal synthesis of strychnine (**1**). The critical element in the design of the synthetic plan was inspired by a transformation in the proposed biogenetic conversion of indole alkaloids possessing the corynantheoid skeleton, which may be represented by **4** and **5**, into alkaloids of the *Strychnos* family such as **2** and **1**, respectively (Scheme 1).[14]

Scheme 1



We recently reported a general entry to indole alkaloids of the heteroyohimboid and corynantheoid families that featured a vinylogous Mannich reaction followed by an intramolecular hetero-Diels−Alder reaction to assemble the pentacyclic molecular framework of these alkaloids.[15] For example, reaction of **6**, which was prepared in two steps from tryptamine, with 1-((trimethylsilyl)oxy)butadiene in the presence of crotonyl chloride (**7a**) gave **8a** that underwent cyclization upon heating to give the pentacyclic adduct **9a** in 70% overall yield from **6** (Scheme 2).

To apply the retrosynthetic analysis adumbrated in Scheme 1 to a concise synthesis of akuammicine (**2**), it was first necessary to convert **9a** into deformylgeissoschizine (**12a**), which is a well-known intermediate in the syntheses of corynantheoid alkaloids. In the event, hydration of the enol ether moiety of **9a** followed by oxidation[16] of the intermediate lactol gave the lactone **10a** in 79% yield. When **10a** was exposed to sodium methoxide, *β*-elimination ensued to give an acid that was esterified *in situ* to give **11a** in 79% yield. Selective reduction of the amide moiety of **11a** proceeded in 91% yield to furnish **12a** in only eight steps from tryptamine. A similar sequence of reactions was performed to prepare the oxygenated analogue **12b** in comparable overall yield.

With the key intermediates **12a,b** in hand, we examined the feasibility of mimicking the biogenetic reorganization of a corynantheoid intermediate into the pentacyclic skeleton of the *Strychnos* family. Treatment of **12a** with *tert*-butylhypochlorite in the presence of SnCl$_4$ gave a mixture of epimeric chloroindolenines **13a** that were not isolated but rather treated directly with lithium hexamethyldisilazide to give a mixture from which (±)-akuammicine (**2**) was isolated in 30−35% yield (Scheme 3). The synthetic **2** thus obtained was identical (TLC, ^{1}H and ^{13}C NMR) with an authentic sample.[17] The oxygenated analogue **12b** underwent a similar conversion to give **16** in about 25−30% yield.

The mechanism of this novel biogenetically-patterned transformation has not been fully established. However, the initial

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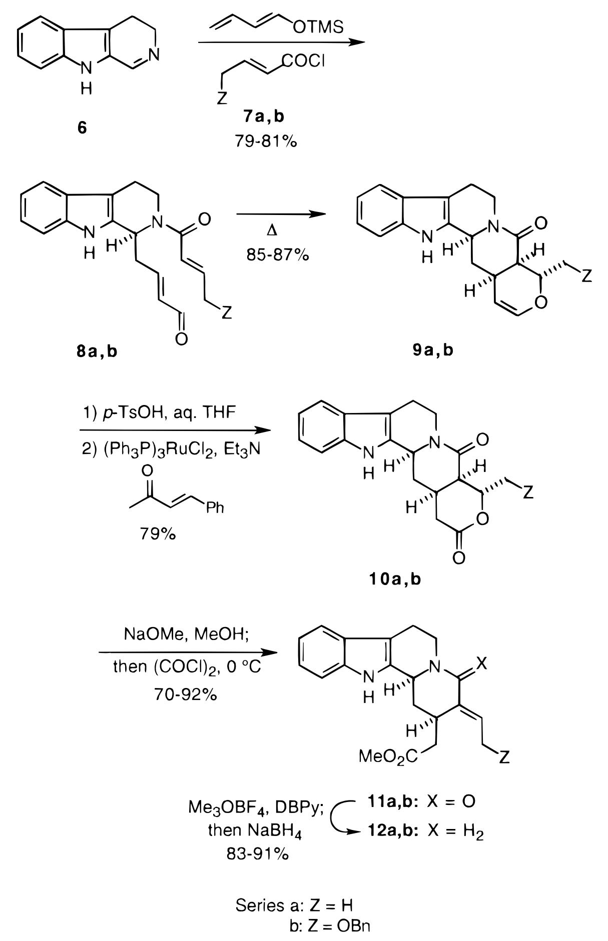
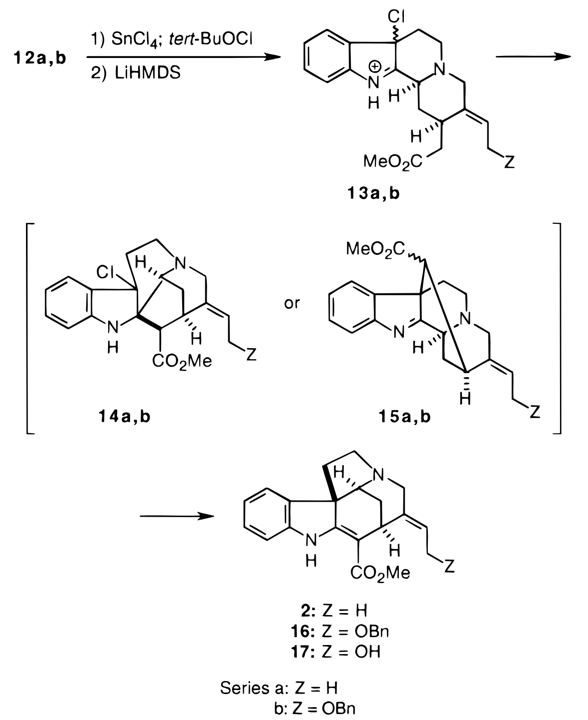
Scheme 2



Scheme 3



oxidation of the indole ring with electropositive halogen to give the chloroindolenines as **13a,b** is well precedented.[18] Treatment of **13a,b** with base is then envisioned to give intermediates related to **14a,b** or **15a,b**, which undergo skeletal reorganization to give **2** and **16**. This hypothesis is based upon the related rearrangements of substituted tetrahydrocarbolines to the *Aspidosperma* skeleton that are also promoted upon sequential reaction with hypochlorite and base.[19] Furthermore, the base-induced rearrangement of strictamine, which is one of the epimeric forms of **15a**, into akuammicine is known.[20] We are presently undertaking experiments to unravel the details of this interesting transformation anticipating that some insights may lead to increased efficiency.[21]

The unprotected alcohol **17** has been converted by Overman in four steps into strychnine (**1**),[7] but several attempts to selectively remove the benzyl protecting group from **16** by hydrogenolysis have been accompanied by significant reduction of the double bond; an alternate hydroxyl protecting group is thus indicated. Although difficulties encountered in deprotecting **16** to give **17** temporarily preclude the claim of a formal synthesis of strychnine, the facile synthesis of **16** provides clear evidence that this route constitutes a novel entry to this complex alkaloid.

An extraordinarily concise synthesis of (±)-akuammicine (**2**) has been developed that requires only 10 steps from commercially available starting materials. The approach is also applicable to the facile synthesis of strychnine (**1**) as evidenced by the preparation of the oxygenated analogue **16**. The synthetic strategy features a biomimetically-patterned transformation of the corynantheoid framework via oxidation and base-induced rearrangement to give the *Akuamma* skeleton as illustrated by the conversions **12a** → **2** and **12b** → **16**. The applications of this and related biomimetic transformations to the syntheses of other indole alkaloids is currently being investigated on a broad front, and the results of these investigations will be reported in due course.

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Supporting Information Available: Complete characterization (^{1}H and ^{13}C NMR and IR spectra and mass spectral data) for all new compounds (3 pages). See any current masthead page for ordering and Internet access instructions.

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[21] As evidenced by following the course of the rearrangement by TLC, it appears that only one of the diastereoisomeric chloroindolenines **12a,b** undergoes the rearrangement with the other remaining unchanged during the course of the reaction. This observation suggests that if the stereochemistry of the chlorination step could be controlled, the overall efficiency of this biomimetic conversion might be significantly improved.