Formal Synthesis of *Aspidosperma* Alkaloids *via* the Intramolecular [3 + 2] Cycloaddition of 2-Azapentdienyllithiums

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Abstract

A formal synthesis of the *Aspidosperm* a alkaloids aspidospermidine, aspidospermine, and quebrachamine is reported through an efficient preparation of Stork's penultimate intermediate. The key step of the sequence involved an intramolecular [3 + 2] cycloaddition of the 2-azapentadienyllithium 21 formed in situ from the corresponding imine 1, which after *N*-alkylation of the resulting cycloadduct, provided 2 in excellent yield. The synthesis represents a new disconnection of the classical tricyclic ketone used for appendage of the requisite indole.

The *Aspidosperma* alkaloids have long been the target of synthetic studies due to their structural complexity and interesting biological activities. To date, more than 250 alkaloids in this family have been isolated[1] and are composed of vastly diverse structural elements with the majority containing the core exemplified by aspidospermidine **3** (Figure 1). Vinblastine has found clinical use for the treatment of various cancers and is comprised of perhaps the most complicated molecular architecture in this family.[2] In contrast, aspidospermidine, the most basic alkaloid to retain the characteristic pentacyclic structure, is not of pharmacological interest and is devoid of sensitive functional groups.[3] For this reason, aspidospermidine has often been used as a sharpening stone for developing new routes to these natural products, thereby resulting in numerous total syntheses.[4] A classic in this area, Stork's synthesis of aspidospermine **4** and quebrachamine **5**, relied on a late stage introduction of the indole moiety onto a tricyclic ketone intermediate (**6a**) prepared by a sequential annulation strategy.[5] Since then, many others have intercepted Stork's route.[6] Aubé[6h,i] and Banwell[6j] have demonstrated that ketone **6b** (Scheme 1, a diastereomer of Stork's intermediate) could also be used in the preparation of aspidospermidine **3**.

As part of an ongoing project aimed at the use of [3 + 2] cycloadditions of 2-azallylstannanes in alkaloid synthesis,[7] we sought to develop a strategy for the efficient preparation of the Stork-type tricycle **6** by a new disconnection. We have previously reported on the preparation of α,β-unsaturated-2-azaallylstannanes and their use in the generation and cycloaddition of 2-azapentadienyl anions and azomethine ylides.[8,9] Cycloaddition of the anions gives products that result from the all-*trans*-2-azapentadienyl anion (the "W" conformation; *vide infra*). We predicted that the resultant pyrrolidines would be synthetically useful because they contain an alkenyl group in the 2-position that provides a handle for further functionalization.

According to the retrosynthetic analysis shown in Scheme 1, it was recognized that **6b** should be attainable using fairly simple precursors. As illustrated, the ketone **6b** should be accessible by reduction of the diene in **7** and oxidation of the corresponding alcohol that results after deprotection. The tricyclic diene **7** would be assembled by an intramolecular Heck reaction

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involving the vinyl iodide **8**. This bicyclic amine **8** should result from an intramolecular cycloaddition of the α,β-unsaturated-2-azaallylstannane **9**. The vinylsilane functionality was employed because it is a much better anionophile than a simple alkene.[10] Further, desilylation should be possible at the stage of the oxidation of the secondary alcohol to an α-silylketone.

The key acyclic imine **9** should be accessible from the corresponding aldehyde and amine by condensation. Examination of the requisite aldehyde suggested the possibility of installing the carbonyl functionality by a Claisen rearrangment, which would also define the olefin geometry. This strategy had previously been employed in a similar system to give the aldehyde **14**[11] (Scheme 2) that should easily be transformed into the key intermediate **9** after some functional group manipulation. To this end, the acetal **11** was formed by protecting 2-bromoacrolein **10** using the conditions reported by Smith (Scheme 2).[12] Multigram quantities of **11** were easily prepared, and following distillation, found to have an excellent shelf life when stored cold. Lithium-halogen exchange was carried out using *n*-butyllithium. The resulting organolithium was quenched with excess acetaldehyde to form the alcohol **12**. Depezay's Johnson orthoester Claisen conditions were used to give the ethyl ester **13**.[11] Although Depezay reported isolating exclusively the *Z* isomer, in our hands the *E/Z* ratio was batch dependent. Fortunately, upon deprotection of the acetal, the aldehyde isomerized to the *E*-α,β-unsaturated aldehyde **14**. Reduction with sodium borohydride in methanol then gave the allylic alcohol **15** in 5 steps and 73% yield from **11**. After protection of the alcohol as the *t*-butyldimethylsilyl ether and adjusting the ester oxidation state, the aldehyde **16** was formed in good yield.

With a good source of **16** in hand, we set out to advance to a suitably protected version of **9** and test the key cycloaddition (Scheme 3). To this end, 1-lithio-1-trimethylsilylethylene was added to the aldehyde **16**, and the resultant alcohol was protected as the BOM ether to give **17** in 86% yield. The BOM protecting group was chosen because it should be cleaved at the same time the diene of **7** (Scheme 1) is reduced by hydrogenation. The *t*-butyldimethylsilyl ether in **17** was removed by treatment with a catalytic amount of *p*-toluenesulfonic acid in methanol to give the alcohol **18** in 87% yield. The alcohol was oxidized to the aldehyde using Dess-Martin periodinane to give the aldehyde **19**, and condensation of the α-stannylamine was effected under standard conditions. After removal of the solvent, the imine **1** was added to a dilute solution of *n*-butyllithium and the cycloadduct **22** was obtained, presumably through chair transition state **21** in which the anion exists in the extended all "W" conformation. After alkylation of the amine with the allyl bromide **23**,[13] the vinyl iodide **2** was obtained in 59% yield from **19**. The stereochemistry of **2** was assigned through a series of NOE experiments.

To complete the formal synthesis, the final ring of the tricyclic ketone **6b** had to be installed and several functional group manipulations carried out. Heck reaction of the vinyl iodide **2** using the Jeffrey conditions established by Rawal for intramolecular reactions on indole alkaloids,[14] gave the tricyclic amine **24** in 43% yield (Scheme 4). Similar yields have been reported on closely related systems.[15] The next step was to reduce the diene by hydrogenation, which should also cleave the BOM protecting group. Several sets of conditions were tried. The reactions were carried out at room temperature in a Parr shaker under a hydrogen atmosphere at 45 psi, while the solvent and catalyst were varied. Using 10% palladium on carbon in THF, ethanol, and methanol with 1 equivalent of trifluoroacetic acid as well as Pearlman's catalyst in ethanol, reduction of both olefins was observed in each case, however BOM deprotected material was never observed. At this point, a two step procedure proved necessary. Under optimized conditions, using 10% palladium on carbon in methanol with 1 molar equivalent of trifluoroacetic acid, the reduction of the olefins was complete in 4 hours, and the TFA salt **25** was obtained in 98% yield.

Deprotection of the BOM group needed to be accomplished by other means. This proved to be a challenging task. Since the product of the reaction would be a β-hydroxysilane which

might undergo a Peterson elimination[16] the choice of reagents seemed crucial. Acyclic β-hydroxysilanes have been studied extensively and it has been found that acid catalyzed elimination proceeds through an antiperiplanar transition state, while the base catalyzed reactions give *syn* elimination products.[16a] Fortunately, given that cyclic structures reduce the degree of conformational mobility, it may be difficult for the system in question to adopt the correct geometry for either acid or base catalyzed olefination to occur.[16a]

Since after deprotection of **25** the resultant hydroxyl group and the silane are *cis*, they cannot adopt an antiperiplanar geometry. To a first approximation, it would seem that acidic hydrolysis of the BOM group would be best suited to this system. However, analysis of molecular models also indicates that while not impossible, it is also difficult to obtain the geometry necessary for the *syn* elimination. Bearing these data in mind, a dissolving metal reduction with lithium in ammonia was first attempted because difficulty was predicted in isolating the product from acidic media. To this end, the salt **25** was exposed to the conditions outlined in Scheme 4.[17] The product of the reaction, which had been followed by GCMS and showed the disappearance of the starting material, seemed to be composed of multiple inseparable products. It was eventually surmised that the additional compound was indeed debenzylated, but the hemiacetal remained and unfortunately was not detectable by GCMS.[18] This was overcome by treating the reduction product with dilute acid in water to liberate the fully deprotected product. Finally, treatment of the β-hydroxysilane with an excess of Dess-Martin periodinane resulted in a mixture of α-silylketone and the desired product **6b**. Once again, exposure of the crude reaction product to dilute aqueous acid gave the ketone **6b** in 54% yield from **25** as the sole product. Analysis of this material provided data identical to spectra provided by Professor Aubé, completing a formal synthesis.

Concise formal syntheses of the *Aspidosperma* alkaloids (±)-aspidospermidine **3**, (±)-aspidospermine **4** , and (±)-quebrachamine **5** were completed by intercepting the classic Stork-type intermediate **6b**. Inclusion of a trimethylsilyl group in the acyclic precurser allows for a smooth cycloaddition and provides the desired cycloadduct as one diastereomer in excellent yield. The product observed is consistent with the chair transition state **21**, demonstrating the predictable nature of the all "W" conformation of this conjugated anion. The synthesis also exemplifies the usefulness of intramolecular cycloaddition reactions of 2-azapentadienyl anions (conjugated 2-azaallyl anions) in complex systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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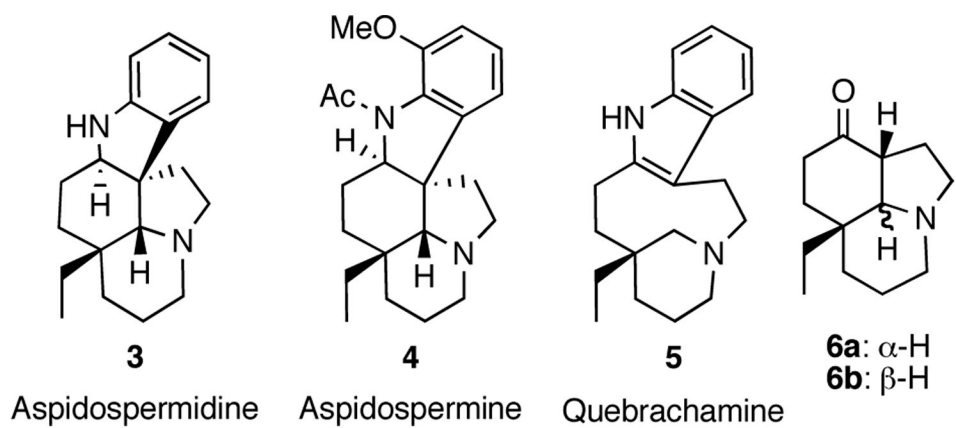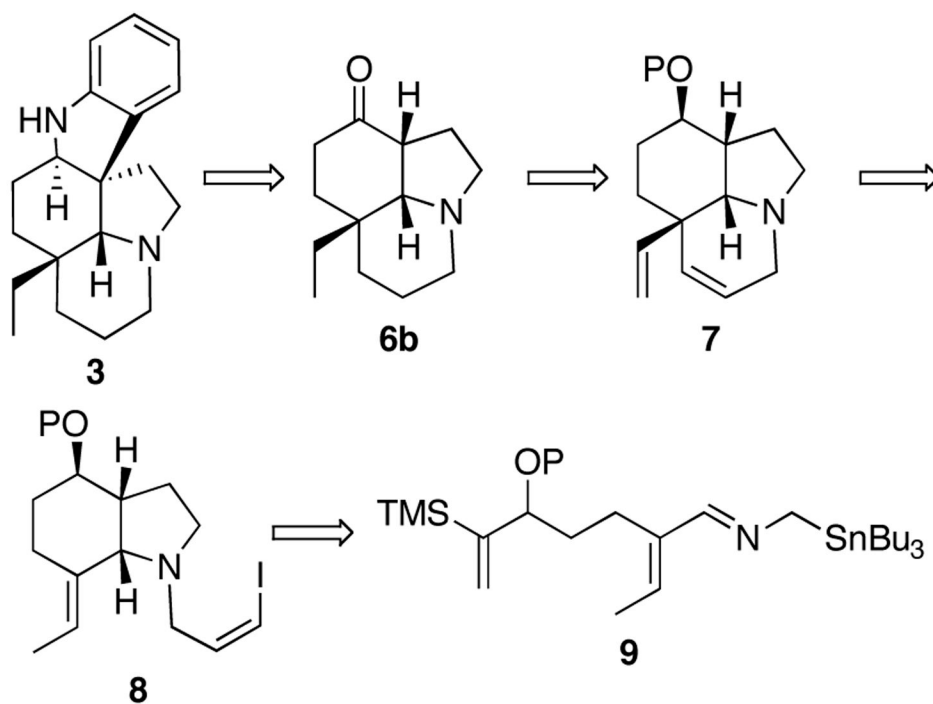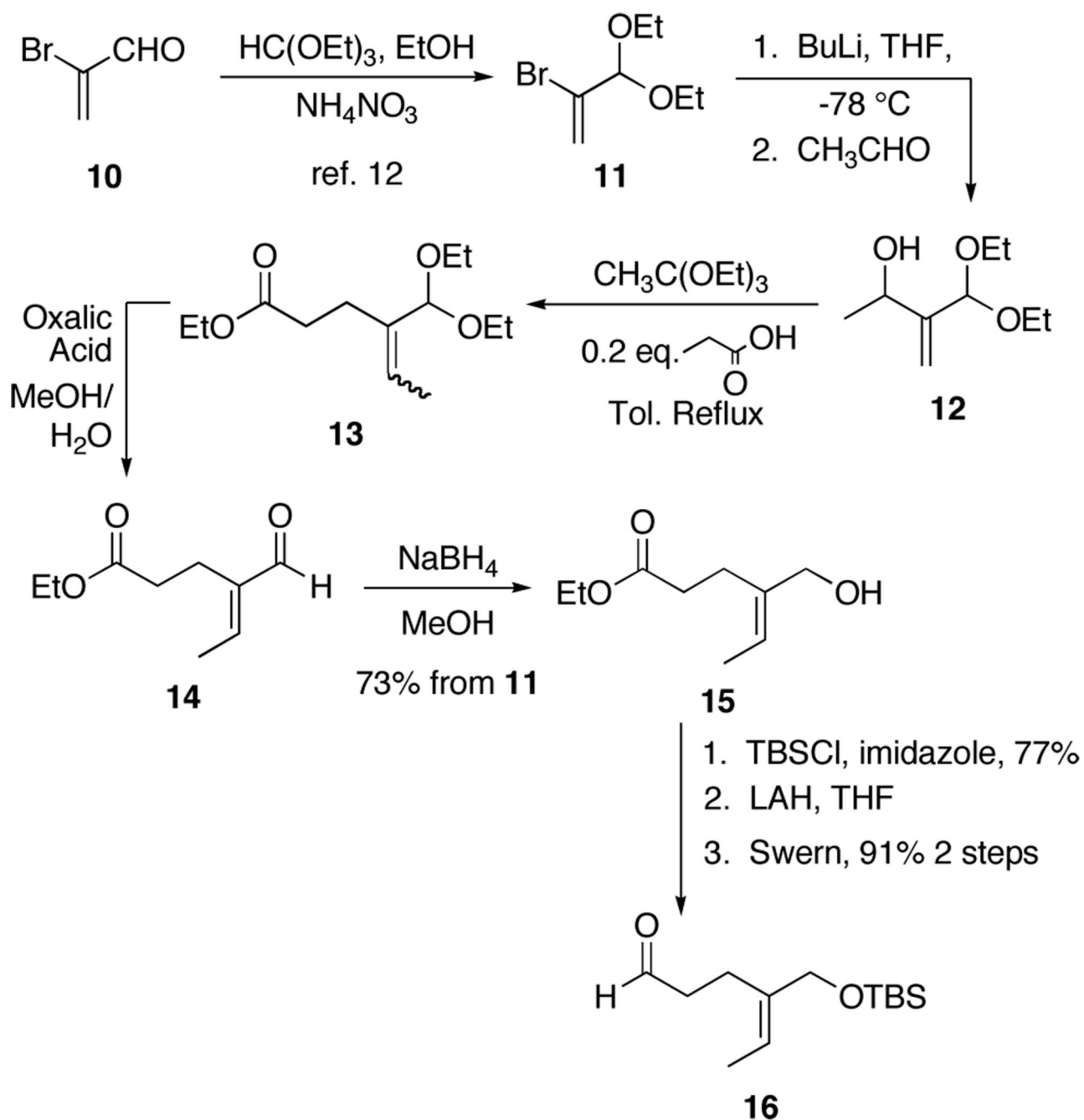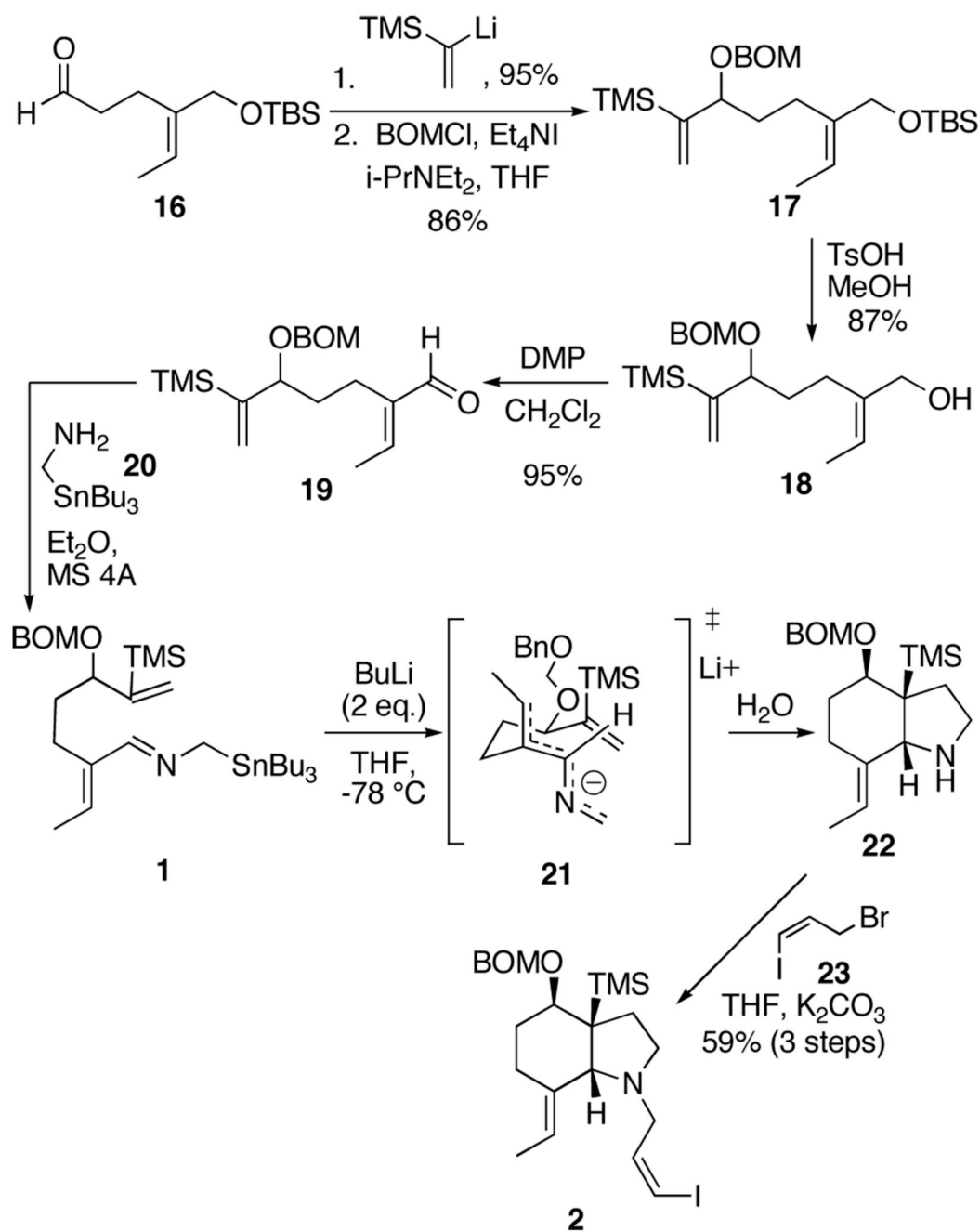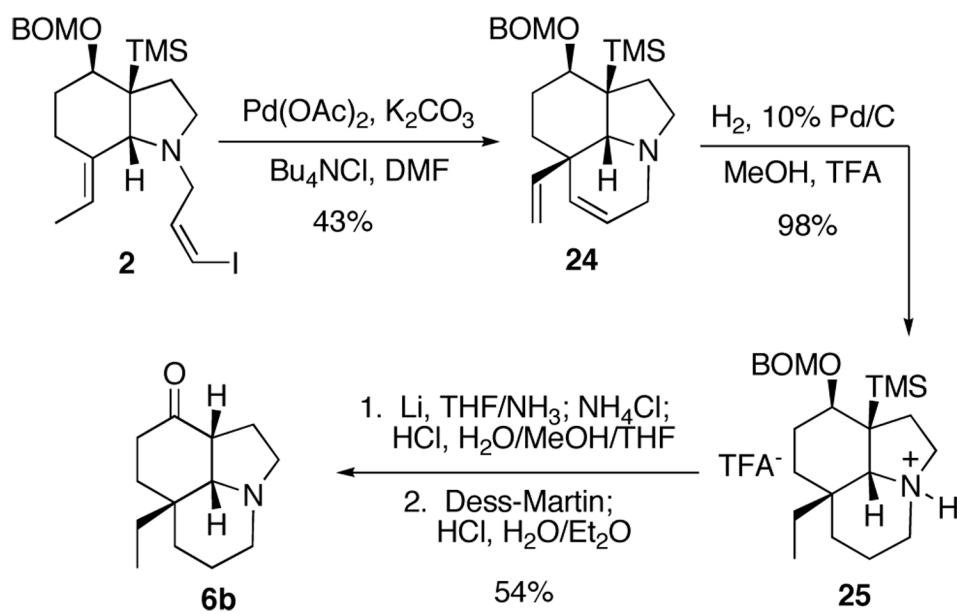
Figure 1.
Aspidosperma Alkaloid Synthetic Targets.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.