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Sequential One-Pot Cyclizations: Concise Access to the ABCE Tetracyclic Framework of *Strychnos* Alkaloids‡

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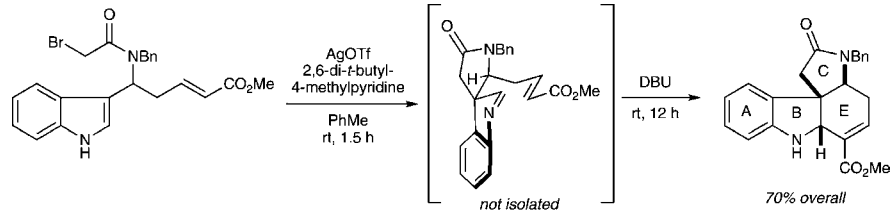
ABSTRACT



sequential one-pot spirocyclization/intramolecular aza-Baylis-Hillman reaction

A sequential one-pot biscyclization route to the ABCE tetracyclic framework of *Strychnos* alkaloids has been developed. Specifically, the AgOTf-mediated spirocyclization of an appropriately functionalized indole 3-carbinamide afforded a stable spiroindolenine intermediate; subsequent addition of DBU to the reaction mixture effected an unprecedented intramolecular aza-Baylis−Hillman reaction, delivering a tetracyclic product in 70% isolated yield.

The indole alkaloids strychnine (**1**)[1] and akuammicine (**2**)[2] are characteristic members of the *Strychnos* family that continue to capture the imagination of organic chemists (Figure 1).[3] Strychnine (**1**) has occupied a special place in the history of synthetic organic chemistry.[4] Woodward's 1954 seminal paper heralded the advent of modern organic synthesis,[5] underscoring the utility of biogenetic hypotheses in guiding strategy irrespective of ultimate veracity.[6] Since then, many groups have reported syntheses of strychnine (**1**),[7] akuammicine (**2**), and related *Strychnos* alkaloids.[8] To be sure, these complex natural products remain excellent substrates for showcasing methodologies aimed at rapidly assembling polycyclic structures in both atom-[9] and step-economical[10] fashion.

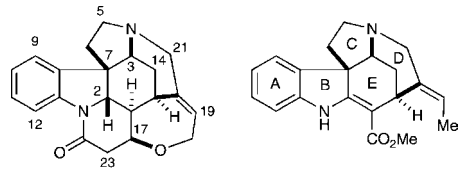


Figure 1. Representative *Strychnos* alkaloids strychnine (**1**) and akuammicine (**2**).

‡ Dedicated to Prof. Frank Davis on the occasion of his 70th birthday.

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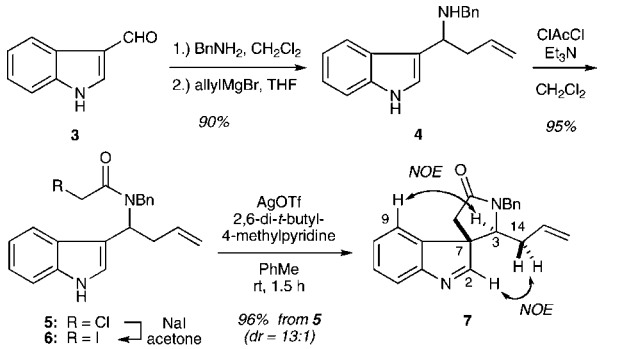
Both alkaloids possess a compact, ABCDE pentacyclic core that harbors three distinct synthetic challenges: (1) the C7 spirocyclic quaternary stereocenter, (2) the bridged CDE framework, and (3) the alkylidene side chain.[7] Herein we report our solution to the first challenge that sets the stage for addressing the remaining two in future work.

Our strategy was inspired by Woodward, who set the C7 stereocenter (and C-ring) early in his synthesis. Taking advantage of indole's nucleophilicity at its C3 position, cyclization of an activated Schiff base to form the C7−C3 bond of **1** furnished a 3,3-spiroindolenine intermediate.[11] We were intrigued at the prospect of also effecting a spirocyclization, albeit on an indole lacking substitution at C2 and cyclizing via the C7−C6 bond.[12] While previous syntheses of *Strychnos* alkaloids have targeted this bond,[13−15] there were no examples of C-ring cylizations *without* the E-ring already in place. Similar trends were found with the related *Aspidosperma* alkaloids.[19,16,17] It was during this latter analysis that we found tactical inspiration from Heathcock's elegant synthesis of aspidospermidine wherein AgOTf was employed to cyclize an iodoacetamide onto a tetrahydrocarbazole scaffold.[18]

To test our idea, we prepared a substrate that would be amenable to further synthetic elaboration. Condensation of commercially available indole-3-carboxaldehyde (**3**) with benzylamine and allylation of the Schiff base afforded homoallylic amine **4** in 90% over two steps (Scheme 1).

Scheme 1. Synthesis of Spiroindolenine **7**

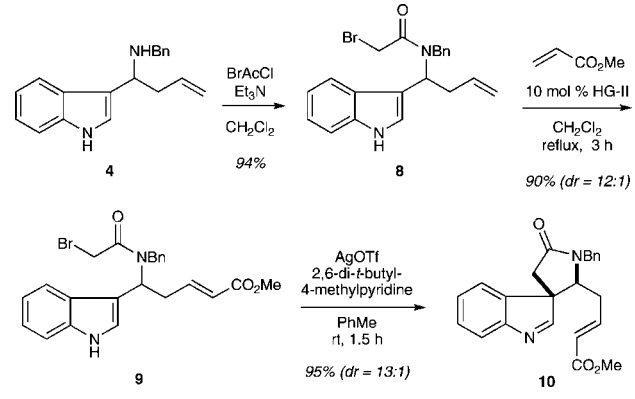


Acylation with chloroacetyl chloride and Et_3N provided chloroacetamide **5** in 95% yield. A Finklestein reaction delivered iodoacetamide **6**, setting the stage for the critical spirocyclization. Examination of molecular models suggested the cyclization of **6** would proceed stereoselectively to furnish an intermediate mapping onto the C-ring of the *Strychnos* alkaloids. In the event, treatment of iodoacetamide **6** with AgOTf and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in toluene at room temperature for 1.5 h cleanly delivered spiroindolenine **7** in 96% yield from **5** (dr = 13:1). The use of base was critical for the success of this reaction. Although we screened other bases (e.g., 2,6-lutidine, pyridine, Et_3N, *i*-Pr_2NEt), DTBMP gave the highest yield. Additionally, the reaction proceeded in both THF and CH_2Cl_2. Stronger bases (e.g., NaH, *t*-BuOK) also cyclized **6** in the absence of AgOTf albeit at the expense of both yield and diastereoselectivity.[19] Finally, the relative stereochemistry of spiroindolenine **7** was secured from a NOE analysis of select hydrogens (C9↔C3 and C2↔C14) in the ^1H NMR spectrum (Scheme 1).

With the C7 stereocenter and C-ring in place, attention was directed at closing the E-ring. Ideally, our approach would segue smoothly into D-ring closure. Rawal's brilliant use of the intramolecular Heck reaction to fashion the D-ring[20] struck us as a suitable candidate; moreover, our route established the requisite C15−C16 olefin in the second step. Cognizant of the electrophilic nature of the spiroindolenine imine and the need for a C17 methylcarboxylate to access targets **1** and **2**, we envisioned the use of an intramolecular aza-Morita[21] or aza-Baylis−Hillman (IABH)[22] reaction of **7** tethered to an enoate (C15−C17) as a viable tactic. To the best of our knowledge, this specific transformation was unprecedented.[23] Furthermore, we wanted to consolidate a step by utilizing a bromoacetamide in place of a chloroacetamide as the latter did not cyclize when subjected to our optimized reaction conditions (i.e., AgOTf and DTBMP).

To realize this goal, we acylated **4** with bromoacetyl chloride to furnish bromoacetamide **8** in 94% yield (Scheme 2). A cross-metathesis reaction was recruited to install the enoate functionality.[24] Phosphine-free Hoveyda−Grubbs II catalyst (HG-II)[25] proved effective for this transformation, affording enoate **9** in 90% yield (dr = 12:1 by LC-MS).

Scheme 2. Synthesis of Enoate-Tethered Spiroindolenine **10**



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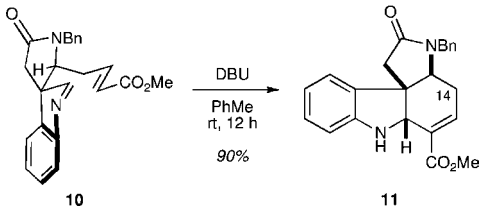
Gratifyingly, the key spirocyclization also proceeded well with bromoacetamide **9**, accessing spiroindolenine **10** in 95% yield (dr = 13:1).

With spiroindolenine **10** in hand, we screened a variety of conditions to effect either the intramolecular aza-Morita or IABH reaction. We observed no reaction of **10** with Bu_3P, Et_3N, *i*-Pr_2NEt, DMAP, or DABCO regardless of solvent used (e.g., CH_2Cl_2, THF, PhMe). However, treatment of **10** with 2 equiv of 1,8-diazabicycloundec-7-ene (DBU) in toluene at room temperature for 12 h cleanly afforded ABCE tetracycle **11** in 90% yield (Scheme 3). The use of less DBU

Scheme 3. Novel Intramolecular aza-Baylis−Hillman Reaction To Close the E-Ring



translated into longer reaction times. Performing the reaction in THF gave **11** in slightly lower yield (83%).

As the more traditional Baylis−Hillman bases did not effect the cyclization irrespective of loading (0.1−2.0 equiv), an alternative mechanistic hypotheses emerged, namely, γ-deprotonation of the enoate by DBU, cyclization, and olefin isomerization.[26] To test this hypothesis, we carried out the same reaction with PhMe that had been saturated with D_2O. If the DBU-promoted deprotonation and attendant cyclization/isomerization sequence was operative, a fraction of deuterium incorporation at C14 (see Scheme 3) should be observed in the ^{1}H NMR spectrum of **11**. In the event, however, we found no such evidence of this taking place. While this experiment does not invalidate the alternate mechanistic hypothesis, it does strengthen the IABH argument.

Recrystallization of tetracycle **11** from EtOAc afforded material suitable for single crystal X-ray analysis. The ORTEP representation of **11** is shown in Figure 2, confirming the structural assignment of the ABCE *Strychnos* tetracycle.

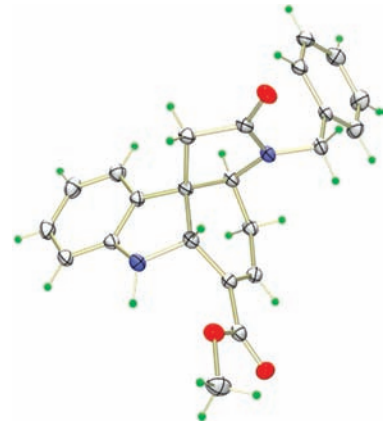
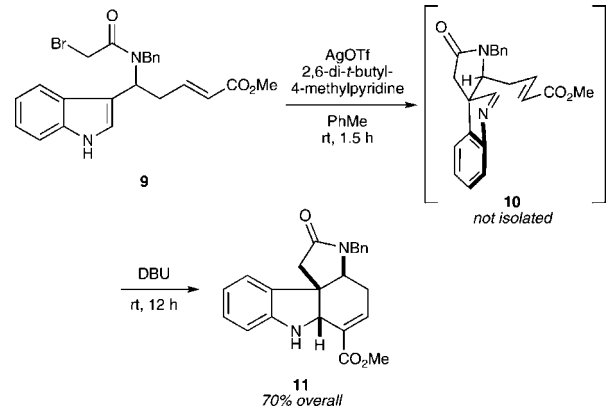


Figure 2. ORTEP of ABCE tetracycle **11**.

Our laboratory has had a longstanding interest in maximizing synthetic efficiency in the context of natural product total synthesis either by deliberately avoiding protecting groups[27,28] or sequencing reactions in a one-pot (tandem) manner to rapidly access useful building blocks.[29,30] By not isolating spiroindolenine **10**, a sequential one-pot version (i.e., **9** → **11**) could be achieved, thus streamlining the synthesis. In the event, treatment of bromoacetamide **9** with AgOTf and DTBMP in toluene at room temperature for 1.5 h followed by the addition of DBU and additional stirring (12 h) afforded **11** in 70% yield after flash silica gel chromatography (Scheme 4).

Scheme 4. Sequential One-Pot Synthesis of **11**



In summary, we have developed a concise and efficient route to the ABCE tetracyclic scaffold **11** of *Strychnos*

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alkaloids (five steps from commercially available aldehyde **3**, 53% overall yield). The route features a novel sequential one-pot spirocyclization/intramolecular aza-Baylis−Hillman reaction that proceeds in 70% overall yield. We are currently investigating the mechanism of the E-ring cyclization and applying our method to the total syntheses of various *Strychnos* alkaloids, in addition to developing an asymmetric variant thereof. Those results will be reported in due course.

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Supporting Information Available: Experimental procedures, characterization of compounds **4**−**7** and **8**−**11** (including ^{1}H and ^{13}C NMR spectra). Crystallograpic details for **11** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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