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# C–H Amination in Synthesis: An Approach to the Assembly of the B/C/D Ring System of Aconitine

**Rosemary M. Conrad and J. Du Bois***

*Department of Chemistry, Stanford University, Stanford, California 94305-5080*

*jdubois@stanford.edu*

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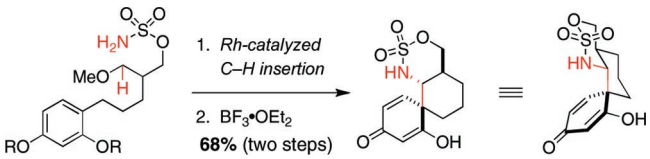
## ABSTRACT




**A strategy for the preparation of aconitine is described that attempts to exploit chemoselective C–H amination and the electrophilic reactivity of oxathiazinane *N,O*-acetals for assembling the complex, polycyclic carbon framework of the natural product.**

Extracts from the *Aconitum* genus of plants have been recognized since antiquity for their potent analgesic and antipyretic properties. The efficacy of these herbal medicines can be traced, in part, to the complex alkaloid aconitine **1** (Figure 1).[1] This topologically intricate natural product is

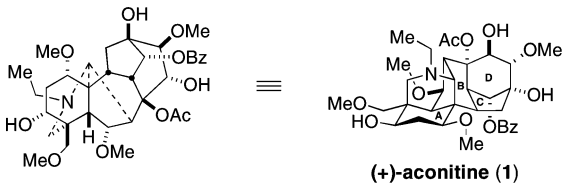



**Figure 1.** A poisonous constituent of the *Aconitum* genus.

one member of a large family of related structures that share a common $C_{19}$ diterpenoid frame.[2] Although the molecular form of aconitine has been known for close to 50 years, no chemical preparation of the alkaloid has been described.[3] Elegant works by Wiesner and co-workers in syntheses of talatisamine, chasmanine, and 13-desoxydelphonine are the only reports detailing the assembly of associated aconane products.[4] From our perspective, aconitine and related alkaloids present an ideal forum to examine methods and to devise strategies for crafting nitrogen-based heterocycles through selective C−H amination.[5] Additionally, an aconitine synthesis presents opportunities for reaction development to access highly oxygenated carbocycles, as exemplified by the D ring of the target. Guided by these two principal aims, we have attempted to exploit the versatile chemistry of oxathiazinane *N,O*-acetals in a synthesis of the natural product. This unique family of heterocycles can be generated through the use of selective C−H amination reactions developed in our laboratory. Under the action of a Lewis acid, intramolecular arene addition to an oxathiazinane *N,O*-acetal would enable simultaneous construction of the A and

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B rings of aconitine. Our efforts to implement this strategy on an advanced model system of the natural product are highlighted herein.

Prior work from our lab has demonstrated that chemoselective C−H insertion of a Rh-stabilized nitrene into an α-ethereal center can be utilized to generate oxathiazinane *N*,*O*-acetal heterocycles such as **3** (Figure 2). In the presence

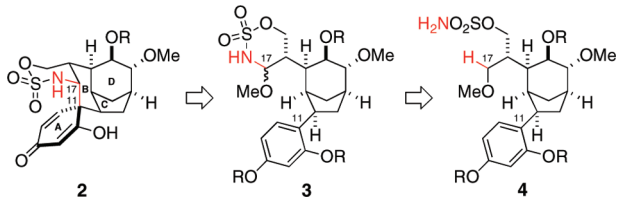

**Figure 2.** A C−H amination route to the aconitine skeleton.

of a Lewis acid and a nucleophilic agent, these novel *N*,*O*-acetal derivatives function as electrophiles to make available substitutionally complex oxathiazinane products.[6] To capitalize on these findings for an aconitine synthesis, a late-stage C−H amination reaction was envisioned that would afford **3**. Treatment of **3** with a Lewis acid would result in the subsequent addition of the pendant aromatic ring to generate spirodienone **2**. The successful implementation of this strategy would make possible installation of both the C17 nitrogen and C11 tetrasubstituted stereocenters (aconitine numbering) as well as the B ring of the carbon skeleton in a single C−C bond-forming event. Importantly, the oxathiazinane moiety serves as a controlling element to ensure the proper stereochemical outcome in the iminium ion addition (vide infra). While prior studies from our lab have shown that allyl silanes, silyl enol ethers, and alkynyl zinc species are effective nucleophiles when employed in coupling reactions with oxathiazinane *N*,*O*-acetals, at the onset of this study, we were uncertain if electron-rich arene groups could function analogously.[7] To test the viability of this plan, two model substrates have been examined.

The first oxathiazinane *N*,*O*-acetal having a tethered aromatic group was formed in straightforward fashion from an available pentanoic acid derivative. Although such a substrate lacks both the C and D ring elements, ease of synthesis rendered it an optimal starting point for our investigations. Oxidative intramolecular C−H insertion of either **5** or **6** under the action of 2 mol % $Rh_2(OAc)_4$ and 1.1 equiv of $PhI(OAc)_2$ afforded the corresponding *N*,*O*-acetals in quantitative conversion and with outstanding chemoselectivity. Subsequent exposure of **7** and **8** to $BF_3{\cdot}OEt_2$ ($CH_2Cl_2$, −78 to 23 °C), however, resulted in considerably disparate outcomes. *N*,*O*-Acetal **7**, having both phenolic oxygens blocked as methyl ethers, gave an intractable product mixture. By contrast, silyl ether **8** furnished the desired spirocycle **11** in 68% yield *and as a single diastereomer*, as determined by proton NMR of the unpurified reaction mixture (Figure 3). Other Lewis acids tested,

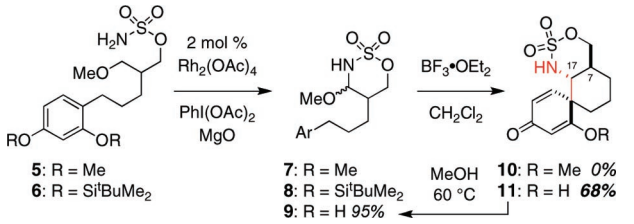

**Figure 3.** A spirodienone is formed from an oxathiazinane *N*,*O*-acetal.

including $Sc(OTf)_3$ and $AlCl_3$, gave similar results, albeit at a cost to the isolated yield of **11**. While we did not explore alternative phenolic protecting groups at this stage of planning, these two data points were quite informative and suggest that deblocking of the phenol must prestage the addition event.

The isolation of **11** as a single diastereomer out of a possible mixture of four is rather striking and deserves comment.[8] We have found that heating **11** in warm MeOH results in C−C bond scission to return the *N*,*O*-acetal and re-aromatized side chain (i.e., **11**→**9**). On the basis of this observation, we speculate that $BF_3{\cdot}OEt_2/CH_2Cl_2$ provides a medium for reversible arene−iminium ion addition and that thermodynamic biases are responsible for controlling the product stereochemistry in **11**.[9] For the purpose of utilizing this reaction sequence in the aconitine synthesis, the relative stereochemistry between C7 and C17 in **11** is, however, incorrect. Accordingly, we wondered whether specific geometrical constraints could be imposed on the linker between the *N*,*O*-acetal heterocycle and the arene ring to force the requisite cis-stereochemistry at positions C7 and C17. The challenge of assembling the rigid C/D ring skeleton of aconitine was therefore assumed. To facilitate the testing of these ideas, a partially deoxygenated form of the C/D bicycle was targeted.

The bicyclooctane frame in **12** restricts the various trajectories by which the arene ring may attack the reactive iminium ion. Based on an analysis of computational models, we reasoned that only one face of the iminium $\pi$-bond would be properly aligned with the aryl moiety to enable successful C−C bond formation. Reaction through this conformer, **12**, affords the requisite cis-oxathiazinane **13**. Rotation around the C7−C8 bond (i.e., **15**) exposes the alternative diastereoface of the iminium ion to the nucleophilic arene. In

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(8) The structure and stereochemistry of **11** have been assigned through $^1H$ and $^{13}C$ HMBC, as well as $^1H$ NOE studies, see the Supporting Information for details.

(9) If the addition reaction were under kinetic control, it is likely that a cis-configuration between C7 and C17 would be favored in accord with predictive models for nucleophilic additions to cyclic iminium ions: Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289.

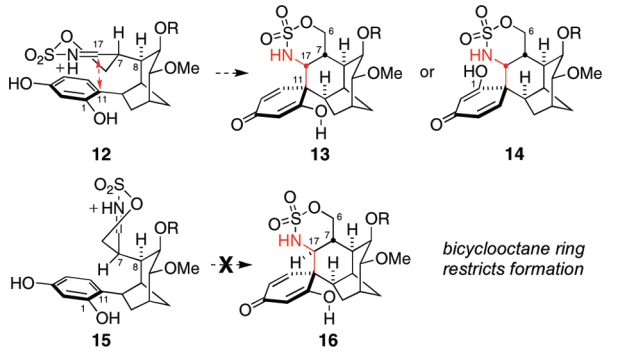



**Figure 4.** Stereochemical analysis of arene addition.

this orientation, the $\pi$-orbital of the iminium ion is situated almost perpendicular to the $\pi$-face of the phenol (Figure 4). Second, the approach of the aryl nucleophile appears to be obstructed by C7−H irrespective the conformation of the iminium ion. If such conjectures prove valid, generation of the undesired C7/C17 trans-isomer **16** is precluded.

A second stereochemical concern that troubles the arene−iminium ion addition involves selectivity at C11. Either face of the prochiral aryl group can potentially attack the iminium ion to furnish isomeric structures, **13** or **14** (or a mixture thereof). Buoyed by the successful coupling of **8** to give a single product, **11**, we were hopeful for a similar outcome to favor **13**. Steric repulsion between the phenolic C1−OH and C6 might serve as a controlling element in this case. As a contigency, however, a symmetrically substituted arene could be used without having to modify significantly the overall synthetic plan.

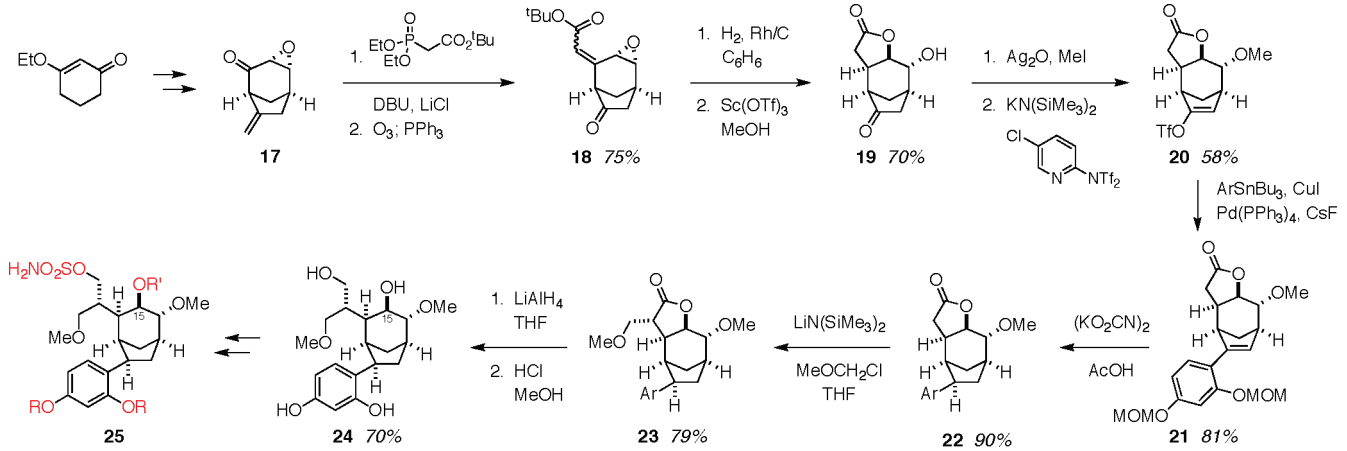
Preparation of a sulfamate substrate containing the C/D rings of the aconitine skeleton was accomplished starting from ketone **17**, a material that is readily accessed from commercial 3-ethoxy-2-cyclohexen-1-one.[10] As shown in Scheme 1, ketone olefination on **17** was performed through a modified Horner−Wadsworth−Emmons reaction to furnish the unsaturated ester as an inconsequential 2:1 mixture of *E*/*Z* isomers.[11] Selective ozonolysis of this intermediate smoothly provided ketone **18** in good overall yield (75%, two steps). Hydrogenation of this product mixture followed by intramolecular epoxide ring-opening with catalytic $Sc(OTf)_3$ afforded lactone **19** as a single diastereomer (70%, two steps). The use of Rh/C in benzene for the reduction of alkene **18** was found to mitigate competing hydrogenolysis of the epoxide.[12] Subsequent alcohol methylation and enol triflate formation proceeded without event.[13]

To further advance lactone **20**, cross-coupling of the aryl group was accomplished with 5 mol % $Pd(PPh_3)_4$ and CuI.[14] Attempts to reduce the aryl olefin by using $H_2$ and supported metal catalysts were, however, unsuccessful and generally returned starting material. Conversely, diimide, formed in situ from the bis-carboxylate salt, reacted smoothly and with perfect diastereocontrol to give the saturated product **22**. At this point, the remainder of the carbon framework could be introduced through lactone α-alkylation with $MeOCH_2Cl$. Analogous to the diimide reduction, enolate alkylation was highly selective, occurring exclusively from the less-hindered, convex face of the tricyclic skeleton. Finally, $LiAlH_4$ reduction of lactone **23** and phenol deprotection gave alcohol **24**.

The flexible nature of intermediate **24** was exploited to generate a small subset of sulfamate structures **25** having different combinations of phenol and C15−OH protecting groups (i.e., silylated phenol groups, esterification of C15−OH). The ability to prepare such compounds was important given our earlier experiences with the cyclization of **7** and **8** (see Figure 3). As we would subsequently determine, though each of the sulfamate derivatives could be made to undergo successful α-ethereal C−H insertion, only one such derivative, **26**, afforded an isolable product following the attempted iminium ion cyclization.

Despite the complexity and degree of attendant functional groups present in sulfamate **26**, treatment with $Rh_2(esp)_2$, $PhI(OAc)_2$, and MgO furnished the *N*,*O*-acetal product **27** in high yield and with exquisite chemoselectivity (Figure 5). Other dinuclear Rh catalysts also promote this transformation, but none were as effective as $Rh_2(esp)_2$.[15] The

**Scheme 1**



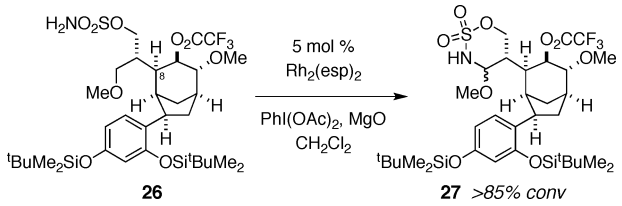



**Figure 5.** Chemo- and regioselective C−H insertion gives the desired *N*,*O*-acetal.

selective generation of *N*,*O*-acetal **27** in this process is quite striking considering the placement of a 3° C−H bond at C8. Such a level of positional control is testament to the sensitivity of the Rh-mediated process to both steric and electronic effects.

While sulfamates such as **26** could be smoothly converted to the corresponding *N*,*O*-acetal, unfortunately, subsequent attempts to induce Lewis acid-mediated cyclization resulted in intractable product mixtures. Different combinations of Lewis acid ($BF_3$·$OEt_2$, $Sc(OTf)_3$) and solvent ($CH_2Cl_2$, $CH_3CN$, $CH_3OH$) failed to improve matters, until it was determined that removal of both the $^tBuMe_2Si-$ and $CF_3CO_2-$ groups followed by $BF_3$·$OEt_2$ treatment could furnish an isolable amount of a new product **33** (∼10%). Extensive $^1H$ and $^{13}C$ NMR, and mass spectral analysis of this compound indicated that the spirodienone had indeed formed. The proximity of the 2° alcohol at C15, however, appears to complicate matters by displacing the incipient oxathiazinane (*path a*). In addition, alkylation of the phenolic−OH was noted. An alternative pathway to **33** could proceed through *N*,*O*-acetal **31** (*path b*). Activation of this intermediate by $BF_3$·$OEt_2$ would generate an oxocarbenium ion **32**, which is then intercepted by the arene group. Phenolic alkylation as in *path a* completes this reaction cascade (Figure 6). Both proposals suggest that protection of the C15−OH could positively alter the outcome of this process. All attempts, however, to perform the iminium ion cyclization in the presence of an appropriate C15−OH blocking group did not prove fruitful.

While the isolated pentacycle **33** is structurally intriguing, it is clearly imperfect as an intermediate toward aconitine. Owing to these collective results, we are forced to re-evaluate

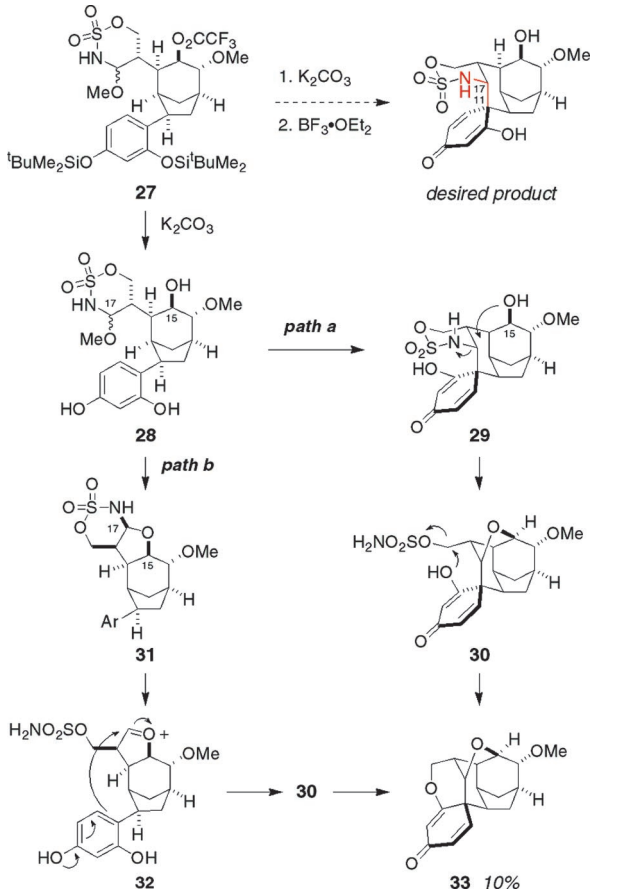



**Figure 6.** An unexpected rearrangement.

our synthetic plan to the alkaloid. Nevertheless, the success of the C−H amination reaction when applied to structures such as **26** (arguably the most complex tested to date) is quite rewarding and gives evidence of the utility of this method for the construction of complex molecules.

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**Note Added after ASAP Publication.** Scheme 1 and Figure 5 contained an error in the version published ASAP on December 1, 2007; the corrected version published on December 4, 2007.

**Supporting Information Available:** General experimental protocols 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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(10) Preparation of **17** is accomplished in five transformations, the details of which are described in the Supporting Information.

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(12) Conditions that were hampered by or led to exclusive epoxide opening included the following: $H_2$ and Pd/C, Pt/C or $PtO_2$ in EtOAc, THF, $Et_2O$ or $C_6H_6$.

(13) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

(14) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132.

(15) (a) $Rh_2(esp)_2$ = $Rh_2(\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionate)$_2$. (b) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (c) Other catalysts that were examined included $Rh_2(OAc)_4$, $Rh_2(O_2CCPh_3)_4$, $Rh_2(O_2CCF_3)_4$, and $Rh_2(O_2CCMe_3)_4$.