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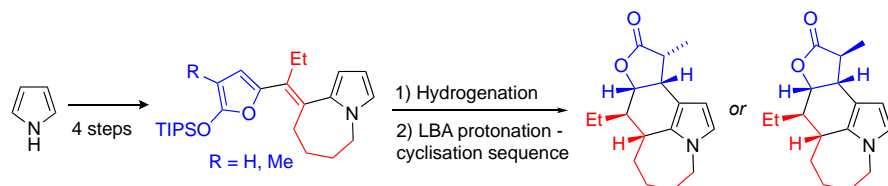
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# A rapid synthetic approach to the ABCD Core of the *Stemona* alkaloids

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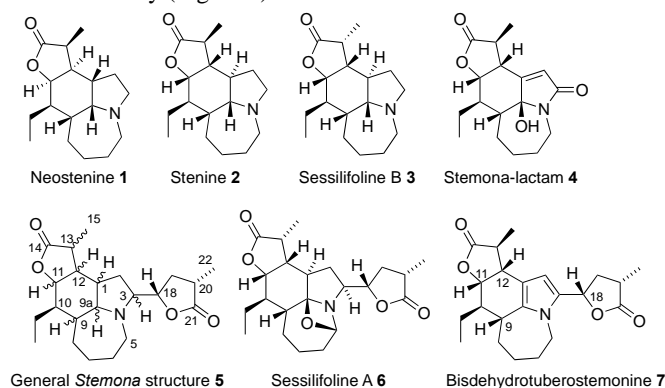


**ABSTRACT:** A new Lewis acid-assisted Brønsted acid cascade approach for the stereoselective formation of the tetracyclic *Stemona* alkaloid skeleton is described in five steps from epoxide **15**. Crucially, this tetracyclic product can be accessed as either C13 epimer, potentially serving as intermediates for the synthesis of a range of *Stemona* alkaloids.

The *Stemona* alkaloids (Figure 1) are a large class of natural product, possessing a wealth of complex stereochemistry as well as potent bioactive properties;<sup>1</sup> such features make them attractive targets to synthetic chemists and medicinal chemists alike. Indeed, a considerable body of work in this area underlines the level of interest,<sup>2,3</sup> as does their continued interest as non-opioid antitussives.<sup>4</sup> Previously, we reported a synthesis of (±)-neostenine **1** employing a [5+2]-photocycloaddition (**8** to **9**) as a key step (Scheme 1).<sup>5</sup> While this provided rapid, protecting group-free access to neostenine, it had the drawback that the route was specific for neostenine only and could not be easily modified to give wider access to other members of the *Stemona* alkaloid family (Figure 1).

suiting for further cyclisation onto the pyrrole ring (Scheme 1). We imagined such an approach would not only give efficient access to the ring system, but could be modified to provide access to a range of *Stemona* alkaloids, for instance to stenine and sessilifoline B directly, as well as sessilifoline A and bisdehydrotoberostemonine following appropriate functionalization of the pyrrole ring. Another key aspect of the approach was the flexibility regarding the stereochemistry of the C<sub>13</sub> methyl group, which we considered could be either installed at the start or introduced later, likely leading to different stereochemical outcomes.

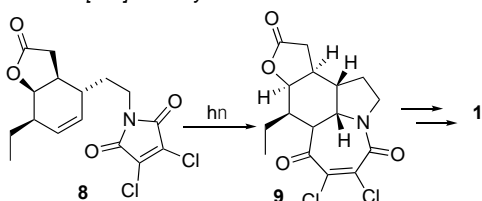
**Scheme 1.** Previous work and revised synthetic approach



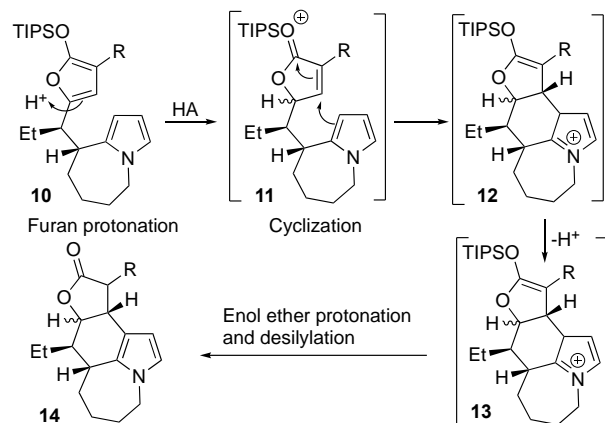
**Figure 1.** Illustrative examples of *Stemona* alkaloids

We therefore considered whether an alternative approach could give access to a common intermediate, thus allowing a more general synthesis of this family of compounds. A revised approach, where selective protonation of TIPS enol ether **10** could generate a reactive Michael acceptor **11**, would be ideally

**Previous work:** [5+2] Photocycloaddition to Neostenine 1

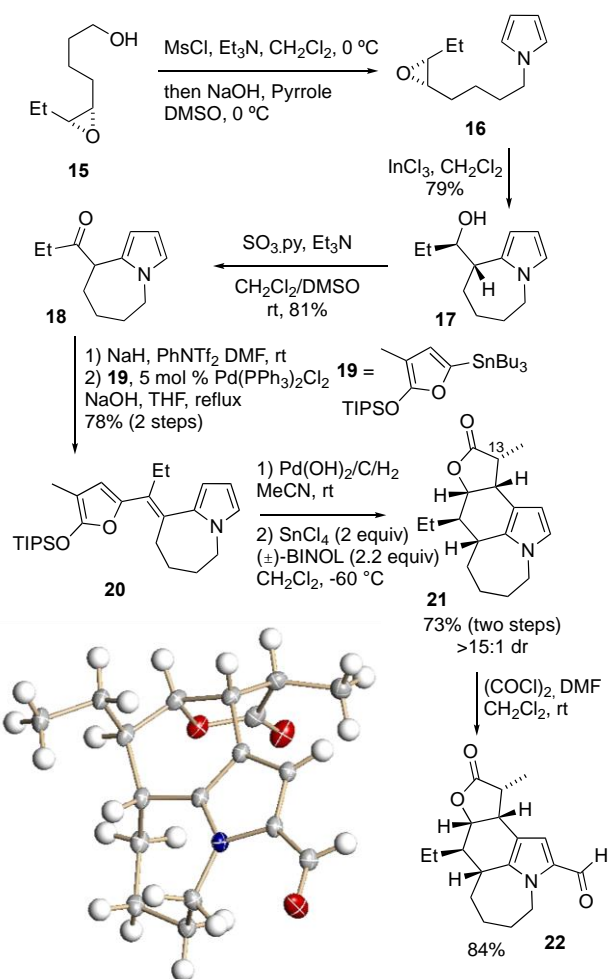


**This work:** Proton mediated activation-cyclization



With this in mind, we set about the synthesis of pyrrole-epoxide **16**. Mesylation and substitution of known<sup>6</sup> epoxy alcohol **15** proved highly successful, yielding 25 g quantities of the epoxide. We then studied a variety of methods for 7-exo cyclisation of the pyrrole onto the epoxide. While boron trifluoride was found to effect this in moderate yield, it was accomplished most efficiently using conditions reported by Banwell,<sup>7</sup> where the use of indium(III) chloride as a Lewis acid furnished **17** as a single diastereomer in high yield. With this alcohol in hand, we next examined its oxidation to the corresponding ketone **18**. This step proved considerably more challenging than we had initially expected, with standard Swern, Dess-Martin, TPAP and Corey-Kim conditions all proving unsuccessful. Nevertheless, we were glad to observe that a Parikh-Doering oxidation<sup>8</sup> did proceed efficiently, and optimization of reaction conditions provided **18** in good yield.

**Scheme 2.** Acid catalyzed polycyclisation route towards the ABCD ring system of the *Stemona* alkaloids



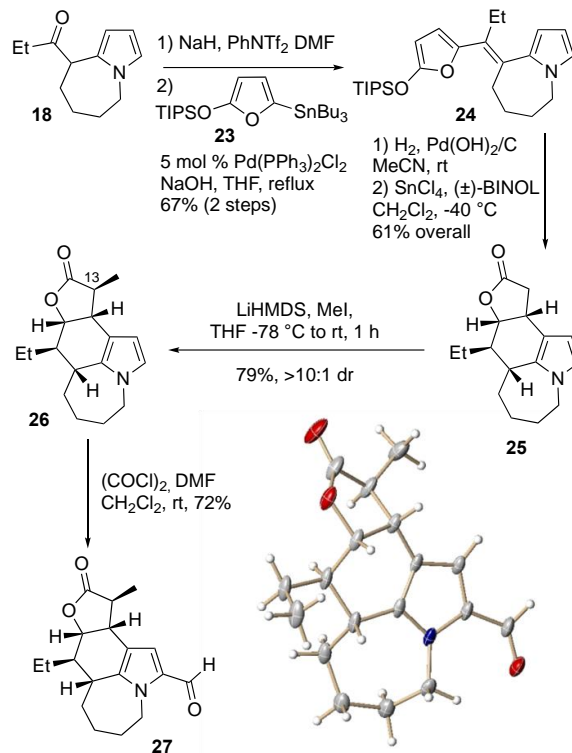
With ketone **18** in hand, we had a range of approaches available to synthesize the furan-pyrrole **20** to investigate the key cyclisation step. After our initial studies, we elected to introduce the furanone fragment via a Stille cross-coupling followed by alkene reduction. To this end, ketone **20** was converted to the corresponding *E*-triflate using sodium hydride and PhNTf<sub>2</sub>. Use of Et<sub>3</sub>N/Tf<sub>2</sub>O gave the *Z*-enol triflate in lower yield and selectivity (4:1). Stille coupling of the crude triflate with stannane **19** proved moderately successful under a range of conditions, but full conversion was not achieved. Stannane activation using sodium hydroxide<sup>9</sup> proved highly successful and gave the cross-coupled product in excellent overall yield from the ketone.

Reduction of the tetra-substituted alkene in **20** proved challenging in the presence of the silyl ether. After some experimentation, it was discovered that this could be effected through the use of Pd(OH)<sub>2</sub>/C as catalyst, however the product was found to be both unstable and difficult to separate from a minor by-product.<sup>10</sup> Consequently this mixture was employed directly in the subsequent key cyclisation step, where regioselective protonation of the silyl enol ether moiety was required to initiate cyclization. We noted that Yamamoto had reported the use of BINOL/SnCl<sub>4</sub>-derived Lewis acid-assisted Brønsted acid (LBA) for related processes,<sup>11</sup> and this was investigated. To our

delight, this resulted in the formation of cyclized product **21**, albeit as a mixture of diastereomers at the  $\alpha$ -methyl position. We reasoned that in fact two equivalents of the LBA should be required for this process, one for cyclisation and a second for stereoselective protonation of the resulting TIPS enol ether. The observed lack of diastereocontrol may therefore result from protonation of the silyl enol ether by an alternative, less bulky acid. Gratifyingly, this hypothesis appeared to be confirmed when increasing to two equivalents led to the formation of **21** as essentially a single diastereomer (15:1) and in good overall yield from alkene **20** (53%). While the diastereomer formed by this process could not be confirmed at this stage, introduction of an aldehyde moiety by a Vilsmeier-Haack reaction led to crystalline product **22**, which was characterised by XRD. This showed the stereochemistry to be that required for sessilifoline A and B, as well as for tubersostemonine and tuberosstemonine A.

Having developed a route to **21** and demonstrated its potential to be functionalized in a manner suitable for the synthesis of a range of natural products, we returned to our initial hypothesis that both epimers at the C13 position could be accessed using this approach. We therefore returned to ketone **18**, again converting this to the corresponding triflate but now performing a Stille coupling with stannane **23**. This proved successful, and hydrogenation was again performed under similar conditions. The subsequent LBA-promoted protonation/cyclisation sequence was again performed on this crude material, although in this case the reaction was found to be significantly more sensitive to temperature than for the formation of methyl-substituted **21**. Fortunately, it was found that good yields could be achieved with sufficient care and the product was again formed in high dr. Interestingly, resubmitting desilylated, uncyclized material from an incomplete reaction to these reaction conditions led to no observed cyclisation, suggesting that the TIPS group is present in an intermediate species, activating the  $\alpha,\beta$ -unsaturated lactone for cyclisation. In fact, all other acids investigated for this cyclisation led to only desilylation, perhaps indicating the uniqueness of the LBA in maintaining the TIPS-oxonium species required for cyclisation.

**Scheme 3.** Acid catalyzed polycyclisation route towards the alternative C13 epimer **25**



At this point, introduction of the  $\alpha$ -methyl group was required, with the intention of obtaining the C13 epimer of **21**. This was performed using LiHMDS followed by MeI and proceeded in good yield and diastereoselectivity to form a compound that was seen to be different to **21** by  $^1\text{H}$  NMR spectroscopy. Again, crystallographic analysis proved impossible due to the oily nature of the compound, and conversion to the corresponding aldehyde via a Vilsmeier-Haack reaction was performed. This provided crystalline material, allowing proof by XRD the desired C13 epimer **27** had been formed.

In conclusion, we have shown that two advanced potential intermediates for the synthesis of a range of *Stemona* alkaloid derivatives can be achieved through the use of Lewis-assisted Bronsted acid protonation-cyclisation sequence as a key step. The yields are high and the synthesis can provide significant quantities of material. We believe the ability to choose which C13 epimer is formed<sup>12</sup> while retaining the same synthetic approach to the series is a considerable advantage, potentially allowing for more thorough medicinal chemistry to be performed on this important class of biologically active natural products. Methods for the stereoselective reduction of pyrroles to pyrrolidines are known,<sup>13,14</sup> potentially allowing broader access to the stenine and neostenine ring systems. Future work will focus on performing an asymmetric reduction of tetrasubstituted alkene **20** to allow the preparation of **21** and **25** in enantiopure form, thus allowing access to a range of natural product structures following either reduction of the pyrrole core or reagent-controlled addition to aldehydes **22** and **27**.

**ASSOCIATED CONTENT**

Experimental procedures and spectroscopic data. This material is available free of charge on the ACS Publications website at DOI: xxxxxx

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