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Synthesis of Demissidine by a Ring Fragmentation 1,3-Dipolar Cycloaddition Approach

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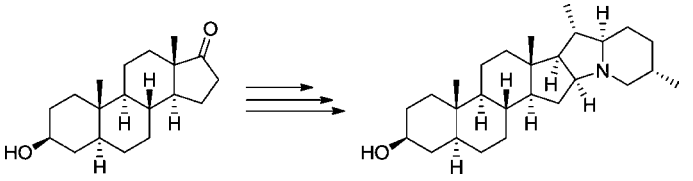
ABSTRACT



A synthesis of the steroidal alkaloid demissidine from epiandrosterone is reported. A ring fragmentation reaction that efficiently ruptured the D-ring of a diazo ester derivative of epiandrosterone to provide an aldehyde tethered ynoate product was key to this sequence. Incorporation of the indolizidine framework was achieved by an azomethine ylide 1,3-dipolar cycloaddition.

The *Solanum* alkaloids are steroidal glycoalkaloids isolated from potatoes and other Solanaceous plants. These toxic alkaloids are known to act as natural insect deterrents,[1] have antimicrobial properties,[2,3] can inhibit acetylcholinesterase,[4] and can disrupt cell membranes.[5] Demissine, commersonine (Figure 1), and their aglycon steroidal alkaloid demissidine (Scheme 1) are the principal alkaloids isolated from several wild potato species including *Solanum demissum*[6] and *Solanum acaule*.[7] Demissidine is structurally similar to solanidine (5-dehydrodemissidine), the steroidal alkaloid aglycon of solanine, the principal alkaloid isolated from *Solanum tuberosum*, the crop potato.

Demissidine was prepared by Kuhn et al.[8] in 1952 and later by Sato and Latham[9] by semisynthesis from the related steroidal alkaloid dihydrotomatidine. In 1963

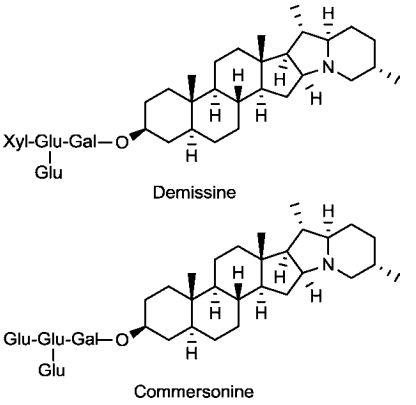


Figure 1. Structure of demissine and commersonine. Abbreviations: Gla = galactose; Glu = glucose; Xyl = xylose.

Adam and Schreiber[10] prepared demissidine in low yields from pregnenolone acetate by addition of 2-lithio-5-methylpyridine followed by unselective hydrogenation and a Hofmann–Löffler–Freytag cyclization. In this letter we report an efficient synthesis of demissidine from epiandrosterone by a sequence that involves a ring

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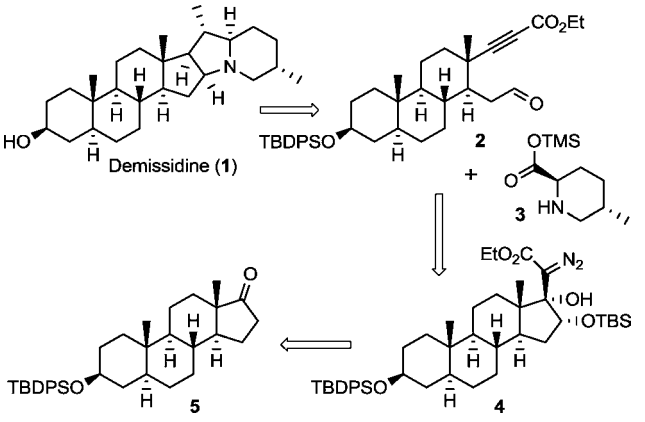
fragmentation and a 1,3-dipolar cycloaddition as key steps.

Our synthetic approach to demissidine takes advantage of our discovery that γ-silyloxy-β-hydroxy-α-diazocarbonyls undergo efficient rupture of the Cγ−Cβ bond in the presence of a Lewis acid to provide tethered aldehyde ynoates or ynones in high yield.[11,12] These bifunctional molecules are excellent precursors for intramolecular azomethine ylide 1,3-dipolar cycloadditions and give polycyclic 2,5-dihydropyrrole products in high yield.[13] As shown in Scheme 1, we envisioned using this sequence of reactions to create the indolizidine framework contained in demissidine. The requisite steroid-based tethered aldehyde ynoate (**2**) would be formed by fragmentation of γ-silyloxy-β-hydroxy-α-diazoester **4**, which in turn could be prepared from epiandrosterone.

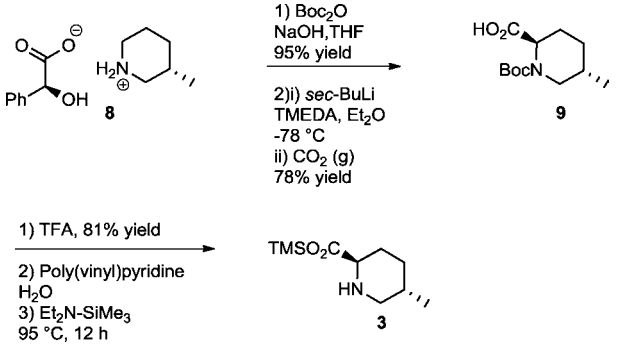
Our synthetic route started from epiandrosterone (**6**), which was converted into α-hydroxy ketone **7** (Scheme 2) by a modification of the procedure reported by Numazawa and Nagaoka[14] for the conversion of epiandrosterone to 16-hydroxy epiandrosterone. This sequence involved a $CuBr_2$ mediated bromination α to the ketone followed by protection of the secondary alcohol as the *tert*-butyldiphenylsilyl ether and subsequent displacement of bromide with hydroxide to provide alcohol **7**. Protection of the free alcohol as the TBS ether and subsequent aldol type addition of ethyl lithiodiazoacetate to the carbonyl provided *syn*-diol **4** in 61% yield over the two steps. Treating diazo **4** with $SnCl_4$ resulted in fragmentation of the steroid's D-ring to provide aldehyde tethered ynoate **2** in 75% yield.

With the requisite dipolar cycloaddition precursor in hand we turned our attention to preparing (5*S*)-5-methylpipecolic acid (Scheme 3). This was most conveniently achieved by resolution of racemic 3-methylpiperidine by cocrystallization with (*S*)-mandelic acid as described by Wong et al.[15] to provide (*S*)-3-methylpiperidine•(*S*)-mandelate in 98% ee.[16] Boc protection of the amine followed by α-lithiation[17−19] and trapping with CO_2 provided *N*-Boc-(2*R*,5*S*)-5-methylpipecolic acid (**9**) in 78% yield as a single diastereomer.[20] Subsequent TFA mediated Boc removal provided the TFA salt of (2*R*,5*S*)-5-methylpipecolic acid in 81% yield. In prior studies[13] we had noted that aldehyde tethered ynoates reacted with amino acids via a decarboxylative intramolecular azomethine ylide 1,3-dipolar cycloaddition more productively when the amino acid component was protected as the trimethylsilyl ester. With this in mind, the TFA salt of the amino acid was passed

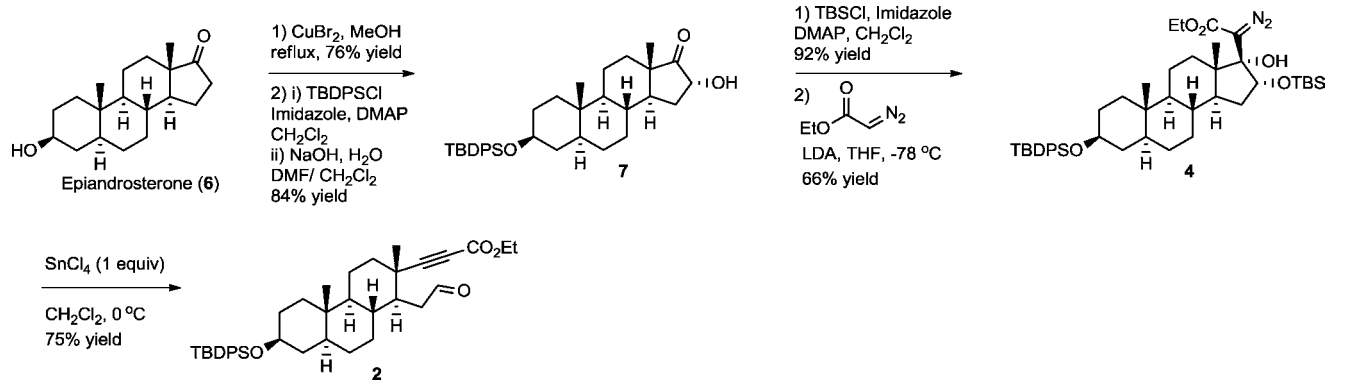
Scheme 1. Retrosynthetic Analysis of Demissidine



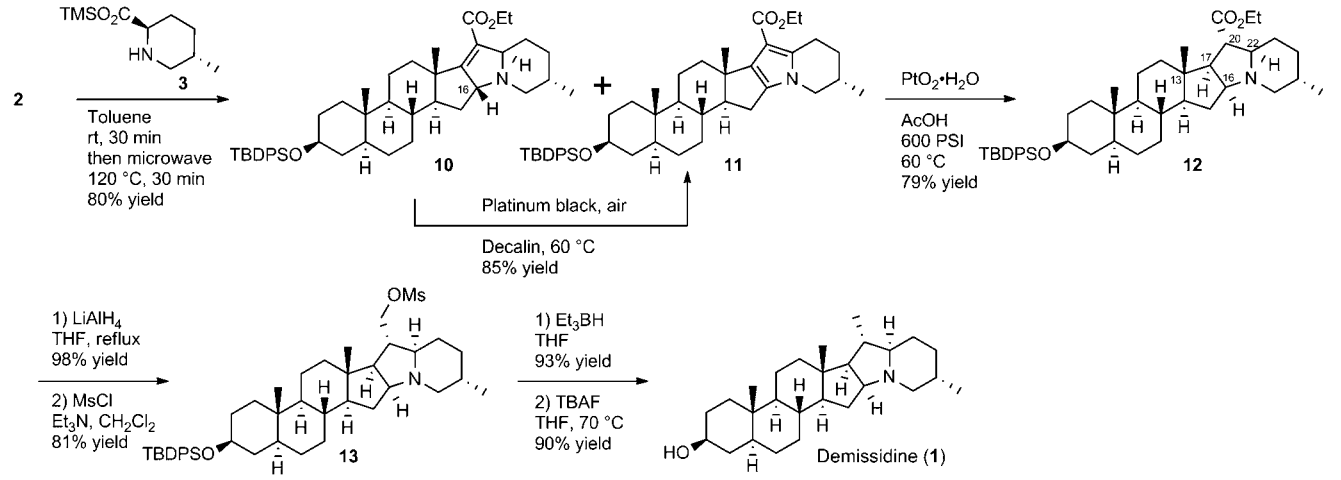
Scheme 3. Preparation of (5*S*)-5-Methylpipecolic Acid



Scheme 2. Preparation of Steroid-Based Tethered Aldehyde Ynoate



Scheme 4. Synthesis of Demissidine



through poly(vinylpyridine) to provide the free base,[21] which was treated with *N,N*-diethyltrimethylsilylamine to give the requisite amino acid silyl ester (**3**).

The key azomethine ylide 1,3-dipolar cycloaddition of aldehyde ynoate **2** and silyl ester **3** proceeded smoothly to provide an easily separable mixture of dihydropyrrole **10** and pyrrole **11** in a combined 80% yield in a ratio that varied from 2:1 to 1:1 (Scheme 4).[22] The formation of dihydropyrrole **10** was exquisitely diastereoselective, but unfortunately provided the product with incorrect stereochemistry at the C_{16} position.[23] Attempts to epimerize the C_{16} vinylogous ester position via deprotonation failed. We reasoned that hydrogenation of the fortuitously formed pyrrole **11** might lead to the corresponding pyrrolidine with the correct stereochemistry at C_{16}, C_{17}, and C_{22} if the angular methyl were to prevent the catalyst from approaching the methyl bearing face. In the event, hydrogenation of pyrrole **11** over PtO_2 in acetic acid at 60 °C and 600 psi provided the pyrrolidine product in a uniquely diastereoselective manner in which all of the protons were delivered from the face opposite the C_{13} angular methyl. We were pleased to note that extending the reaction time led to in situ epimerization at C_{20} and provided the desired pyrrolidine product **12** in which all the stereocenters were set correctly. Although pyrrole **11** is presumably formed by air oxidation of dihydropyrrole **10** during the 1,3-dipolar cycloaddition reaction, attempts to increase the yield of pyrrole **11** by extending the reaction time in the presence of oxygen failed. However, platinum black[24] dehydrogenated dihydropyrrole **10** to provide pyrrole **11** in 85% yield.

To complete the synthesis of demissidine, the ethyl ester was reduced by lithium aluminum hydride to the corresponding primary alcohol in 98% yield, which was in turn converted to mesylate **13** in 81% yield. Reductive cleavage of the mesylate by lithium triethylborohydride proceeded in 93% yield to give the requisite methyl at position C_{20} of the steroid. Removal of the silyl protecting group occurred in 90% yield to provide demissidine.

In summary, demissidine has been synthesized from epiandrosterone. This synthetic approach takes advantage of a Lewis acid mediated fragmentation of a γ-silyloxy-β-hydroxy-α-diazoester to provide a tethered aldehyde ynoate. This key intermediate was successfully used in a subsequent azomethine ylide 1,3-dipolar cycloaddition to provide the indolizidine framework present in the natural product.

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(22) The dipolar cycloaddition was conveniently run in a CEM Corporation Discover series microwave reactor in a sealed reaction vessel. The reaction temperature and pressure are controlled by the reactor.
(23) The relative stereochemistry at C16 was assigned based on the oberservation of a positive NOE between the C16 proton and the angular methyl at C13.
(24) Platinum black was formed by suspending platinum oxide in decalin under an atmosphere of hydrogen gas for 2 h. The dark black solid was isolated by filtration, placed under vacuum overnight, and then exposed to air for 1 h before use.

of Vermont) for assistance with NMR characterization. This work was financially supported by the NIH (National Institute of General Medical Sciences Award Number R01GM092870) and was made possible by use of a facility supported by the Vermont Genetics Network through Grant Number 8P20GM103449 from the INBRE Program of the National Institute of General Medical Sciences (NIGMS), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIGMS or NIH. The National Science Foundation supported this work through instrumentation grants CHE-1126265 and CHE-0821501.

Supporting Information Available. Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.