COMMUNICATION

Revised Structures of Dehydrostenines A and B: Total Syntheses of (±)-Dehydrostenine A and Structure Assigned to Dehydrostenine B

Wesley J. Olivier, Nigel T. Lucas, Alex C. Bissember,* Jason A. Smith,*

Abstract: The first total syntheses of the *Stemona* alkaloid dehydrostenine A and the structure assigned to dehydrostenine B have been completed from a simple pyrrole substrate in 10 and 11 steps, respectively. Two independent Brønsted-acid-mediated intramolecular Michael additions were exploited to construct the tetracyclic dehydrostenine core. As a result of our synthetic studies and associated analysis of the relevant literature, we propose revisions of the structures originally assigned to dehydrostenines A and B.

The *Stemona* alkaloids are a class of diverse polycyclic natural products isolated from plants belonging to the genus *Stemona.* The structures of many *Stemona* alkaloids feature a bicyclic pyrrolo[1,2-a]azepine core in addition to several other fused or otherwise attached rings. Examples, such as stenine (**1**) and sessilifoliamide C (**2**), were first isolated from *Stemona tuberosa* and *Stemona sessilifolia*, respectively (Figure 1).[1,2] Stenine (**1**) has received particular attention as a target for total synthesis, with over 25 reported total or formal syntheses of this natural product completed to date.[3,4] Stenine-type alkaloids are known to exhibit a variety of biological activities and stenine possesses significant acetylcholinesterase activity, for example.[5]

Dehydrostenines A (**3**) and B (**4**) are stenine-type alkaloids in the pyrrole oxidation state, which were isolated from a plant species classified as *Stemona sessilifolia* in 2017 and it appeared that these molecules had not yet succumbed to synthesis when we started our study.[6] The publication detailing the isolation and characterization of these natural products assigned the structure of dehydrostenine A as compound **3** (Figure 1). The stereochemical assignment of the C9-carbon was derived from conclusions drawn from NOESY correlations. Interestingly, the same report included the X-ray crystal structure of this natural product, which instead revealed a structure consistent with the C9- epimer (i.e., structure **5**).[6] Given these issues, we wanted to clarify this discrepancy by validating the structure of dehydrostenine A (**5**) via total synthesis. We were also interested

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       https ://doi.org/10

in preparing the reported structure of dehydrostenine B (**4**), as this would allow us to corroborate the structural and stereochemical assignments for this natural product that were inferred from 1D and 2D NMR spectroscopic data.[6]
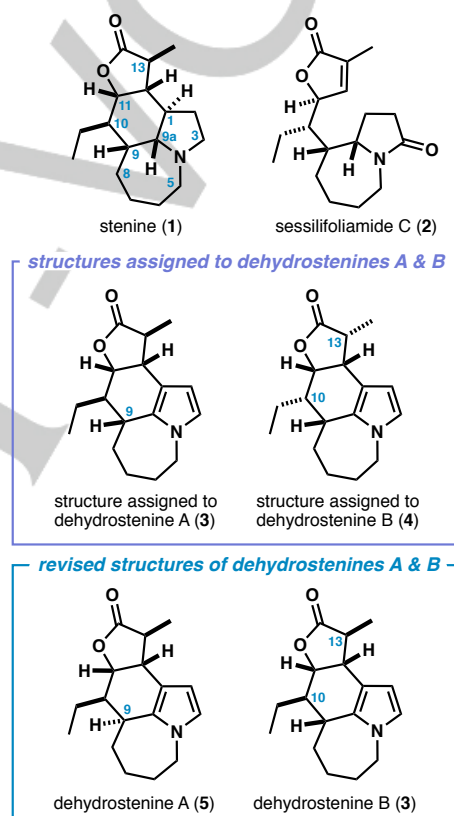

Figure 1. Examples of *Stemona* alkaloids.

We recently reported unified total syntheses of sessilifoliamides C (**2**), B, and D from a pyrrole substrate.[7] Because these bicyclic natural products feature structural similarities to dehydrostenine A, we anticipated that we could access structure **5** by germane chemistry. Specifically, we proposed that pyrrole **7**, which bears a pendant α,β-unsaturated lactone, could be accessed from a common (early-stage) pyrrole intermediate from which we prepared the sessilifoliamides (Figure 2).[7] Furthermore, we posited that lactone **7** could be treated with a Brønsted acid to construct the tetracyclic dehydrostenine framework (**6**), via an intramolecular conjugate addition.[8] This would represent an original general approach to accessing the tetracyclic core of stenine-type alkaloids. Booker-Milburn and coworkers employed a somewhat similar end-game strategy to forge the dehydrostenine core that involved selective

protonation and cyclization of a pyrrole tethered to 2-silyloxyfuran.[9] However, the authors' experimental observations suggest that this cyclization proceeds via a silylated lactone (and not a protonated lactone) intermediate.[9] An unrelated approach for the construction of the dehydrostenine framework has also been reported.[10] By design, our strategy focused on developing a pathway that would also allow for the divergent synthesis of the structure assigned to dehydrostenine B (**4**) for the reasons outlined earlier.

Herein, we report the first total synthesis of dehydrostenine A (**5**) and propose its revised structure. In addition, we synthesized the structure originally assigned to dehydrostenine B (**4**).[6] Consistent with our findings and analysis of relevant and complementary synthetic studies by Booker-Milburn and coworkers,[9] we propose the revised structure of dehydrostenine B (**3**).

Because our proposed approach to assembling tetracycle **6** was unprecedented, prior to embarking on our synthesis of dehydrostenine A (**5**), we evaluated the viability of the centerpiece intramolecular Michael addition using model C-10 desethyl substrate **8** (see Supporting Information).[11] This provided the corresponding tetracyclic pyrrole efficiently and exclusively in only 4 steps from **10**, which galvanized us to apply this strategy to target natural product **5**. Our synthesis commenced from commercially available pyrrole **9**, which was converted to pyrroloazepine **10** in two steps and 59% yield on a two-gram scale as we have previously reported (Scheme 1).[7] α-Ethylation of ester **10** provided pyrroloazepines **11a** and **11b** in a 3.5:1 ratio in 77% combined yield employing optimized conditions. We also explored whether diastereoselective ethylation of ester **10** might be better facilitated from a derivative featuring a chiral auxiliary, however, this was not successful (see Supporting Information). The respective relative configurations of previously reported compounds **11a** and **11b**[7] were tentatively assigned on the basis that major diastereomer **11a** would derive from delivery of iodoethane to the less hindered face of the enolate derived from substrate **10**.
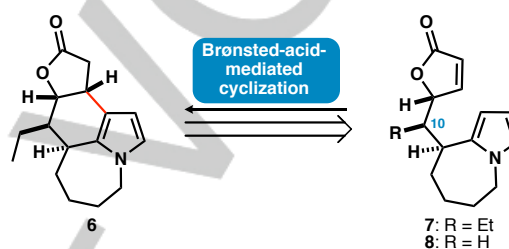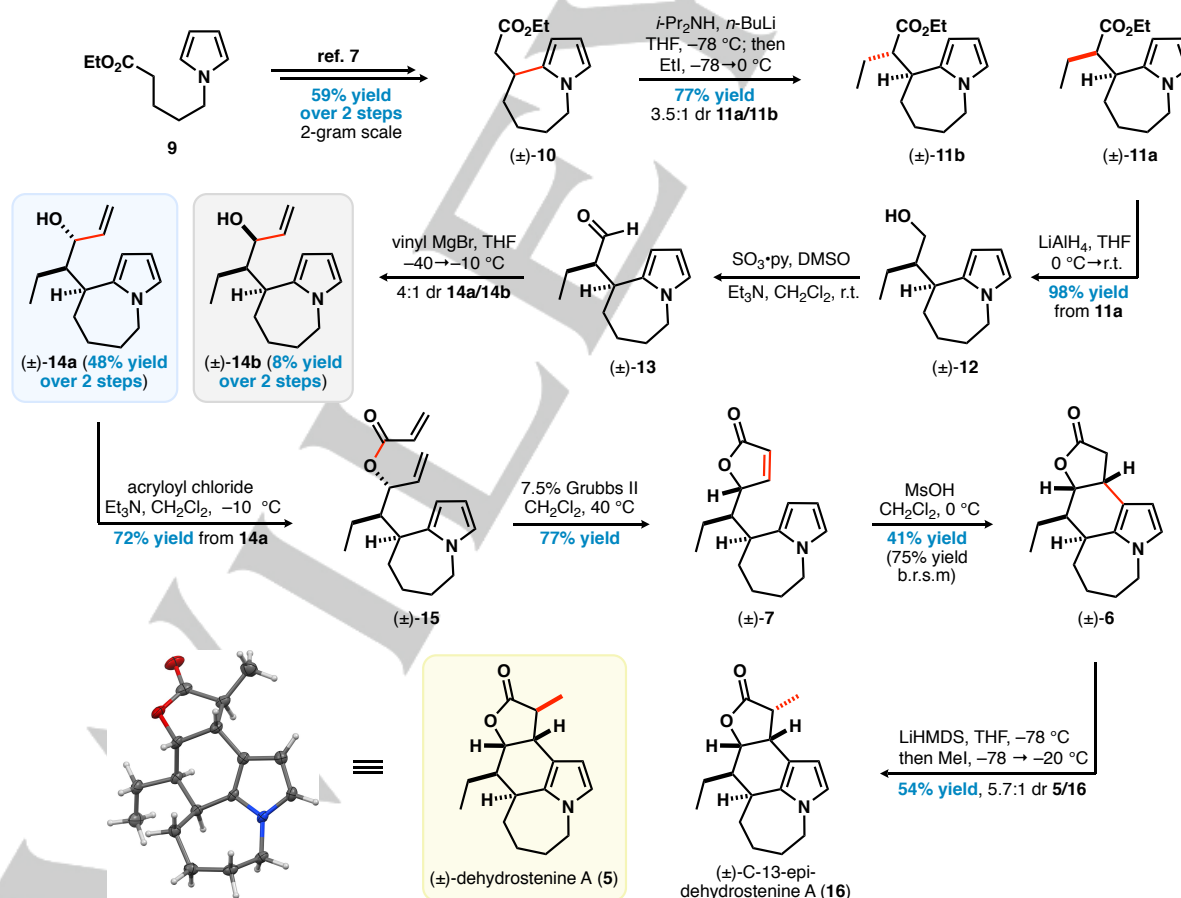

Figure 2. Strategy for constructing the tetracyclic core of dehydrostenine A (**5**).

Scheme 1. Total synthesis of dehydrostenine A (**5**) from commercially available pyrrole **9**.

We intended to selectively reduce ester **11a** to aldehyde **13** and anticipated that this could be achieved directly via treatment with DIBAL-H. However, alcohol **12** was the only product obtained under these conditions.[12] These issues prompted us to reduce ester **11a** to alcohol **12** with LiAlH$_4$ and obtain aldehyde **13** by oxidation. Because hypervalent iodine reagents, such as 2-iodoxybenzoic acid (IBX) and Dess–Martin periodinane, do not offer the required chemoselectivity in the presence of pyrroles,[7,13] we attempted to prepare aldehyde **13** via standard Swern conditions. Although this resulted in decomposition, a Parikh–Doering oxidation successfully delivered aldehyde **13**.[14,15] Product **13** was immediately treated with vinylmagnesium bromide to furnish vinyl alcohols **14a** and **14b** in a 4:1 ratio and 56% combined yield over two steps.[16] The respective relative configurations of **14a** and **14b** were tentatively assigned with reference to the stereoselectivity observed in the reaction of vinylmagnesium bromide with the pyrrolidinone analogue of aldehyde **13**.[7] Major diastereomer **14a** is consistent with delivery of the nucleophile to the less hindered face of aldehyde **13**.

O-Acylation of alcohol **14a** with acryloyl chloride, followed by ring-closing metathesis (RCM) with Grubbs second generation catalyst furnished α,β-unsaturated lactone **7** in 55% yield over the two steps. MsOH-mediated annulation of lactone **7** furnished tetracycle **6** exclusively in 41% yield (75% yield based on recovered starting material).[17] We propose that the observed *cis*-selectivity derives from the higher ring strain associated with the *trans*-fused analogue of lactone **6,** which disfavors formation of the latter diastereoisomer. Comprehensive NMR analysis of tetracycle **6** supported our tentative assignments regarding the relative configurations of synthetic precursors.[9] Subsequent methylation completed the synthesis of target **5** and C13-epimer **16** in a 5.7:1 ratio. We confirmed structure **5** by single crystal X-ray crystallography.[18] The spectroscopic and crystallographic data obtained for compound **5** were consistent with equivalent data for the isolated natural product (see Supporting information).[6]

It should be noted that the structure originally assigned to dehydrostenine A (**3**) was synthesized by Booker-Milburn and co-workers. These researchers also secured the relative configuration of this structure via single crystal X-ray crystallography of C3-formylated derivative **17** (Figure 3).[9] As expected, the spectroscopic data for isolated dehydrostenine A is not consistent with equivalent data for structure **3** reported by

Booker-Milburn and coworkers (see Supporting Information).[6,9] When these findings are taken together, it is evident that the correct structure of dehydrostenine A is molecule **5** (i.e., the C9-epimer of the originally assigned structure (**3**).[6]

Interestingly, through this process we also noted that the NMR spectroscopic data for aforementioned structure **3** reported by Booker-Milburn and co-workers conspicuously matched equivalent data reported for dehydrostenine B in the original isolation study (see Supporting Information).[6,9] This revealed that the structure originally assigned to dehydrostenine B (**4**) was also incorrect. Furthermore, it highlighted that Booker-Milburn and coworkers accomplished the first total synthesis of dehydrostenine B (**3**) in 2019.[9]
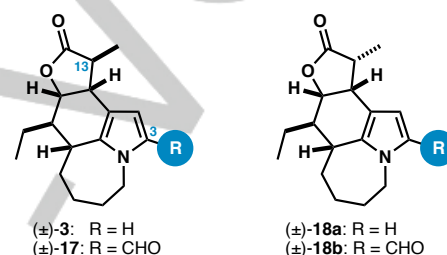
Figure 3. Compounds **3**, **17**, and **18** synthesized by Booker-Milburn and coworkers; structures **17** and **18b** were secured by single crystal X-ray crystallography.[9]

We aimed to prepare target **4** to gain further evidence that the structure assigned to dehydrostenine B (**4**) was incorrect. Our initial attempt commenced from major vinyl alcohol diastereoisomer **14a** (Scheme 2). This involved the S$_N$2 substitution of major vinyl alcohol **14a** with methacrylic acid under Mitsunobu conditions, which inverted the C11-stereocenter, followed by RCM. The Mitsunobu reaction was particularly inefficient.[19] Unfortunately, the key intramolecular Michael addition did not furnish target **4**. In the presence of either MsOH and TfOH, we did not detect the cyclization product and only decomposition of substrate **20** was observed.[20,21] This suggested that a more viable route to the structure assigned to dehydrostenine B (**4**) would involve cyclization from a substrate analogous to heterocycle **7** that did not feature the methyl group.
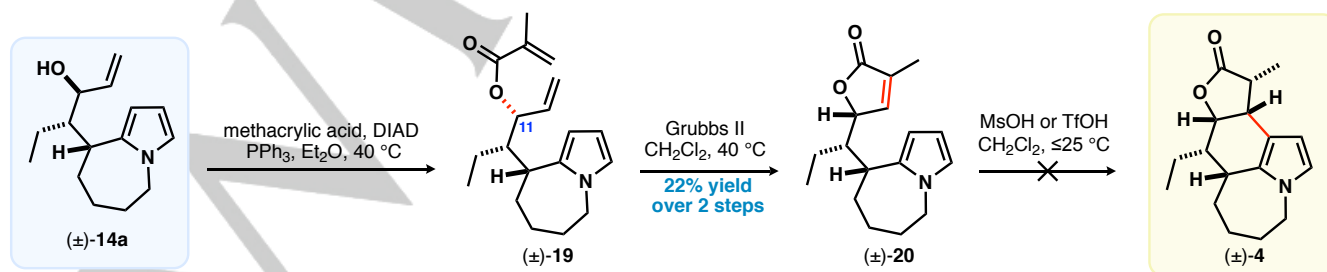

Scheme 2. Attempted synthesis of the structure assigned to dehydrostenine B (**4**) from major diastereomer **14a**.

Our revised attempt to access the structure assigned to dehydrostenine B (**4**) employed minor vinyl alcohol diastereoisomer **14b** and followed an analogous route to the one that delivered dehydrostenine A (**5**) from **14a** (Scheme 3). Thus, O-acylation of alcohol **14b** with acryloyl chloride and RCM of ensuing acrylate ester **21** provided furanone **22** in 56% yield over 2 steps. α,β-Unsaturated lactone **22** was treated with MsOH to afford tetracycle **23** in high yield. Methylation of substrate **23**

exclusively furnished heterocycle **24**, which is the C13-epimer of target **4**. In comparison, methylation reactions performed on diastereomers of molecule **23** (**6** and the desmethyl derivative of **3**) give mixtures of C13-epimers.[9] We anticipate that the high selectivity of this alkylation stems from the exclusive delivery of the methyl group from the less hindered β-face of the enolate derived from molecule **23** as the α-face of this structure is essentially inaccessible (Figure 4).
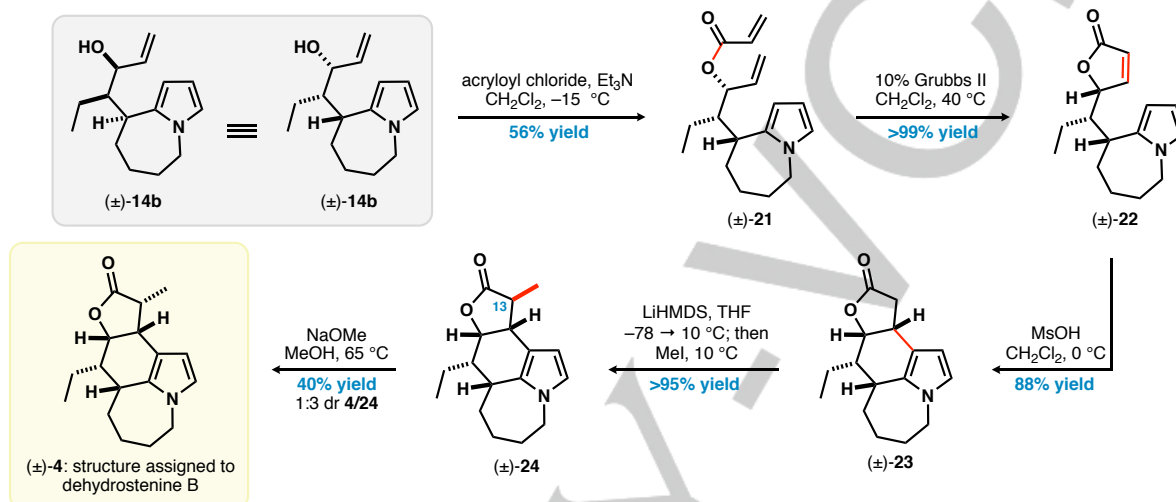
Scheme 3. Synthesis of the structure assigned to dehydrostenine B (**4**) from minor diastereomer **14b**
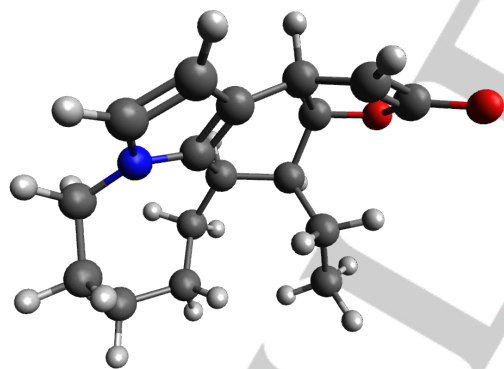
Figure 4. Simulated molecular representation of the enolate derived from substrate **23**.

We attempted to epimerize compound **24** under basic conditions at (or below) ambient temperature, employing LiHMDS, NaOMe, and KH, respectively.[22] Unfortunately, each of these experiments only returned C13-epimer **24**. We propose that the C10-ethyl group effectively shields the α-face of the bowl-shaped substrate to block deprotonation and, hence, the required enolate cannot be generated at low temperature. However, heating molecule **24** with NaOMe in methanol delivered the structure assigned to dehydrostenine B (**4**) and substrate **24** in a 1:3 ratio.

As we anticipated, the spectroscopic data we obtained for compound **4** were not consistent with equivalent data for isolated dehydrostenine B (see Supporting information).[6,23] As we noted earlier, NMR spectroscopic data for structure **3** reported by Booker-Milburn and co-workers clearly matches equivalent data reported for isolated dehydrostenine B,[6,9] which demonstrates that these researchers accomplished the first total synthesis of dehydrostenine B by a particularly elegant and efficient approach.[9] When our work and the aforementioned complementary synthetic studies undertaken by Booker-Milburn and coworkers are taken together, we propose that the correct structure of dehydrostenine B is molecule **3**.

In conclusion, we have completed the first total syntheses of the *Stemona* alkaloid dehydrostenine A and the structure assigned to dehydrostenine B in 10 and 11 steps, respectively. The tetracyclic core of these alkaloids was prepared via an end-game strategy involving a conjugate addition of a pyrrole onto a pendant α,β-unsaturated lactone. As a result of our investigation, we have addressed the stereochemical discrepancy in the literature regarding dehydrostenine A and have reassigned the relative configuration of dehydrostenine B in accordance with our findings and analysis of the relevant literature.[6,9,24]

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

Keywords: dehydrostenines • total synthesis • pyrrole • *Stemona* alkaloids
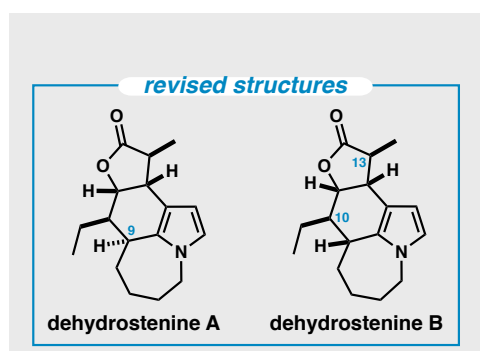
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[11]   Substrate **8** was one of a number of pendant Michael-acceptors that we evaluated in this transformation. However, α,β-unsaturated lactone **8** was the only system that allowed us to construct the core of the target framework efficiently.

[12]   In contrast, treatment of ester **10** (the desethyl analogue of ester **11a**) with DIBAL-H successfully provided the corresponding aldehyde (see Supporting Information).

[13]   (a) J. K. Howard, C. J. T. Hyland, J. Just, J. A. Smith, *Org. Lett.* **2013**, *15*, 1714–1717. (b) I. A. Andreev, N. K. Ratmanova, A. M. Novoselov, D. S. Belov, I. F. Seregina, A. V. Kurkin, *Chem. – Eur. J.* **2016**, *22*, 7262–7267.

[14]   Similar observations concerning the utility of Swern and Parikh–Doering oxidations were made by Booker-Milburn and coworkers in related studies (ref. 9).

[15]   The oxidation of alcohol **12** to rather unstable aldehyde **13** was more efficient and reproducible when performed on a 150–200 mg scale in comparison to experiments performed on larger scales (>500 mg).

[16]   Products **14a/14b** were formed in 3:1 dr when the Grignard addition was conducted at 0 °C. We thought we could convert **14a** to **14b** via oxidation to the ketone and subsequent reduction, however, this route was not feasible (see Supporting Information).

[17]   We observed that molecule **6** is prone to decomposition under the reaction conditions over prolonged periods of time. It is likely that the slow reaction of **7** to **6**, compared to the efficient reaction of **22** to **23** (vide infra) derives from the significant differences in the respective three-dimensional structures of more planar tetracycle **6** in comparison to bowl-shaped tetracycle **23**.

[18]   CCDC 2091223 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[19]   We investigated varying the temperature, solvent, stoichiometry of reagents/reactants, and concentration, but were unable to develop a more efficient Mitsunobu reaction with methacrylic acid and substrate **14a**. We also conducted a Mitsunobu reaction with **14a** and *p*-nitrobenzoic acid, which has been reported to increase the yield of this transformation with sterically hindered alcohols. While this modification greatly enhanced consumption of **14a**, the formation of by-products significantly compromised the efficiency of this route. For selected reports on the use of *p*-nitrobenzoic acid in Mitsunobu reactions see: (a) S. F. Martin, J. A. Dodge, *Tetrahedron* **1991**, *32*, 3017–3020. (b) J. A. Dodge, J. I. Trujillo, M. Presnell, *J. Org. Chem.* **1994**, *59*, 234–236.

[20]   We observed similar patterns of reactivity in analogous intramolecular Michael additions of N-tethered pyrrole substrates in synthetic studies targeting sessilifoliamide natural products. Thus, this somewhat unexpected attenuation of reactivity provided by α-alkyl substituents within these systems likely has a common fundamental basis. Investigating this reactivity in more detail is the subject of future work.

[21]   We expected protonation of the enol intermediate from the more accessible β-face would deliver compound **4** by this approach based on relevant observations from Booker-Milburn and coworkers (ref. 9).

[22]   In the conversion of sessilifoliamide B to sessilifoliamide D, NaOMe (or K_2CO_3 in MeOH) epimerized analogous α-methyl lactones (ref. 7).

[23]   For completeness, we compared the respective NMR spectroscopic data for other synthetic diastereomers of structure **4** (compounds **5** and **24**) that we prepared in our study to equivalent data for isolated dehydrostenine B (ref. 6). We also compared the NMR spectroscopic data for diastereomer **18a** synthesized by Booker-Milburn and coworkers to equivalent data for isolated dehydrostenine B (refs. 6 and 9). In each case, the NMR spectroscopic data did not match the reported data for dehydrostenine B as expected (see Supporting Information).

[24]   We contacted the corresponding authors of the study reporting the isolation of dehydrostenines A and B (ref. 6) who agreed with the revised structure of dehydrostenine A (**5**) that we have proposed (personal communication with Prof. Z.-D. Yang, August 2021).

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revised structures

dehydrostenine A   dehydrostenine B

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Page No. – Page No.

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