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Unified Total Syntheses of (±)-Sessilifoliamides B, C, and D

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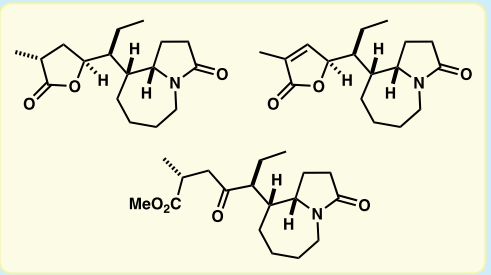
ABSTRACT: The first total syntheses of the *Stemona* alkaloids sessilifoliamides B and D and the second synthesis of sessilifoliamide C have been completed from a simple pyrrole substrate. The bicyclic lactam core was prepared on a gram scale via a Brønsted acid mediated cyclization and controlled oxidation with Dess−Martin periodinane. This delivered sessilifoliamide C (and its C-11 epimer) in 24% yield over 11 steps, and sessilifoliamides B and D in 13 and 17 steps, respectively.



The sessilifoliamide natural products are a class of polycyclic, lactam-containing alkaloids isolated from *Stemona sessilifolia* and other plant species belonging to the genus *Stemona*.[1−6] Sessilifoliamides A−D (**1**−**4**) were first isolated in 2003 and were the first sessilifoliamide-type alkaloids discovered (Figure 1).[1] These natural products are structurally related by a common pyrrolo[1,2-*a*]azepine core.

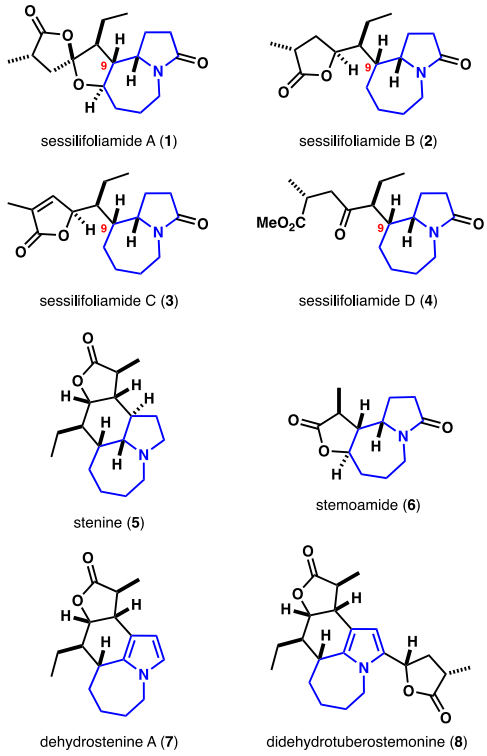


Figure 1. Examples of representative *Stemona* alkaloids.

Sessilifoliamides B−D each possess unique C-9 side chains; however, sessilifoliamide A features a fused spirocyclic acetal. While related *Stemona* alkaloids such as stenine (**5**) and stemoamide (**6**) have garnered considerable attention as targets for total synthesis,[7,8] conspicuously few approaches to sessilifoliamides A−D have been reported. To date, two total syntheses of sessilifoliamide A and one total synthesis of sessilifoliamide C have been published.[8c,9,10] Sessilifoliamides B and D have not yet succumbed to synthesis. Bioactivity studies are yet to be conducted on sessilifoliamides B−D, and thus, accessing these alkaloids synthetically would enable the biological activity of these natural products to be comprehensively evaluated for the first time.

Wipf and Hoye's pioneering total synthesis of enantioenriched (−)-sessilifoliamide C (**3**) realized the target in 18 steps and commenced from chiral glutamic acid derivative **9** (Figure 2A).[10] The construction of the azepine ring was achieved via ring-closing metathesis (RCM) of a 4-pentenyl-5-vinylpyrrolidinone. Further elaboration of this intermediate, including a key Ireland−Claisen rearrangement of a silyl ketene acetal, provided bicyclic lactams **10** as a mixture of diastereomers in 14 steps from pyrrolidinone **9**. Ester **10a** was then efficiently converted to sessilifoliamide C in four steps, which involved a second RCM reaction to construct the lactone ring.

Pyrroles featuring pendant electrophilic moieties are known to participate in intramolecular cyclizations to afford bicyclic heterocycles such as 5,6,7,8-tetrahydroindolizines and pyrrolo[1,2-*a*]azepines.[8c,11,12] This includes annulations via intra-

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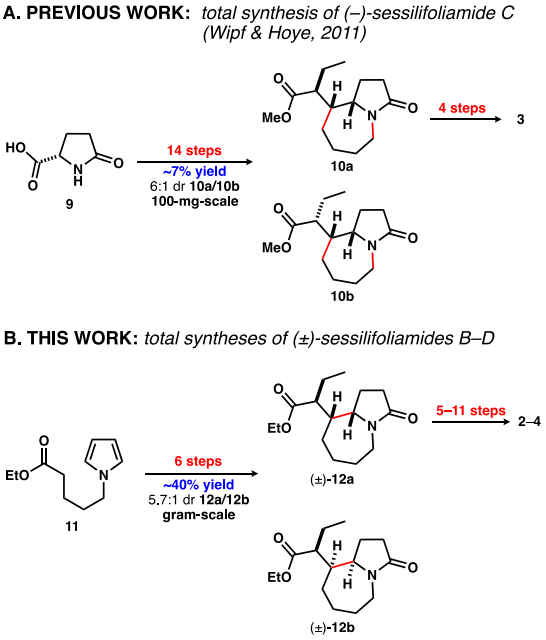


Figure 2. Overview of the successful total syntheses of sessilifoliamides B–D (**2**–**4**).

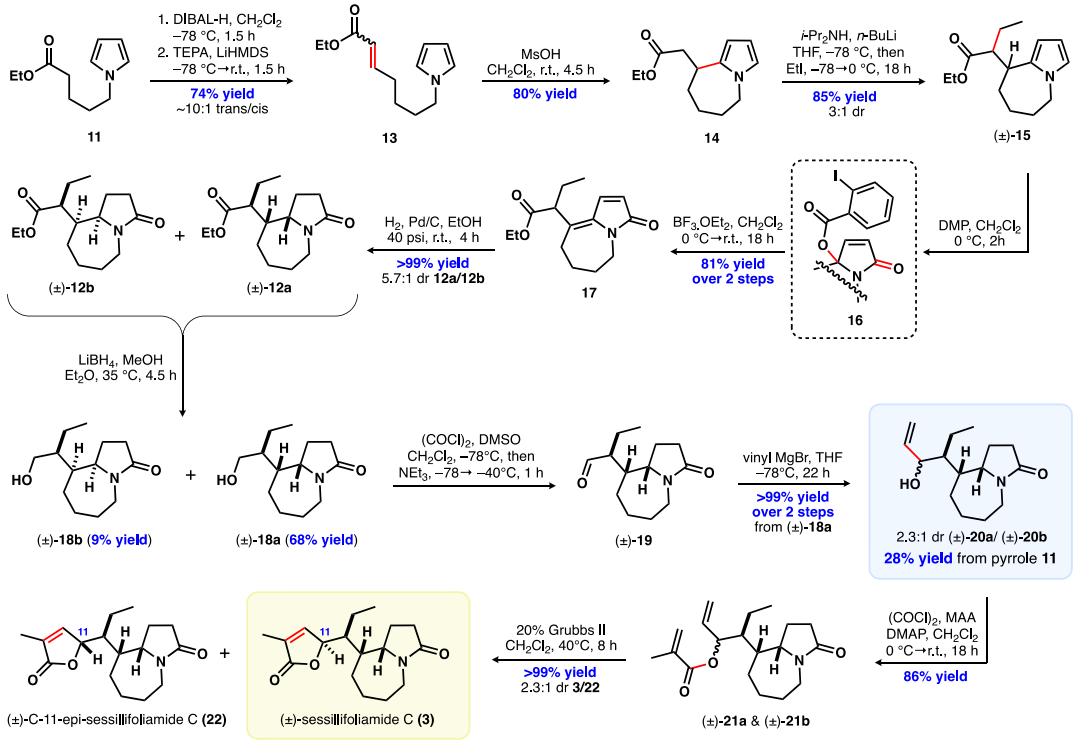
molecular Friedel–Crafts-type acylations and alkylations, oxidative arylations, conjugate additions, and palladium-catalyzed couplings.[11] Pyrrole rings are also amenable to both reduction and (controlled) oxidation which provides access to pyrrolidines and γ-lactams, respectively.[13] These properties should enable pyrroles to serve as attractive substrates from which total syntheses of polycyclic *Stemona* alkaloids can be effected (Figure 1). Despite the considerable interest this family of natural products has attracted as synthetic targets,[7,8] to our knowledge, only a handful of total syntheses of *Stemona* alkaloids have employed pyrrolic compounds as starting materials or key intermediates.[8c,14]

From our experience using conjugate addition chemistry to form bicyclic pyrroles,[15] we reasoned that substrate **11** could facilitate expeditious total syntheses of sessilifoliamides B–D by an original approach (Figure 2B).[16] More specifically, this derived from our findings that pyrrolo[1,2-*a*]azepine architecture can be efficiently constructed via the Brønsted acid mediated intramolecular annulation of pyrrolic α,β-unsaturated esters.[15c] Furthermore, we anticipated that γ-lactam (±)-**12a** could be accessed by deploying Dess–Martin periodinane (DMP) for the controlled oxidation of an appropriate bicyclic pyrrole precursor using our established methodology.[17]

In this report, we confirm the viability of our above-mentioned strategy which enabled the gram-scale synthesis of the bicyclic core of sessilifoliamides B–D {(±)-**12**} and culminated in total syntheses of (±)-sessilifoliamides B–D.

Our synthesis commenced with the one-pot reduction of ester **11** with DIBAL-H, followed by Wadsworth–Emmons olefination of the ensuing aldehyde with triethyl phosphonoacetate (Scheme 1). This provided α,β-unsaturated esters **13** in 74% yield. The Brønsted acid mediated cyclization of substrates **13** was facilitated by methanesulfonic acid and furnished pyrroloazepine **14** in 80% yield.[15c,18] The lithium enolate of ester **14** was then treated with ethyl iodide to provide C-alkylated product **15**. Pleasingly, oxidation of pyrrole **15** with DMP,[17] followed by the elimination of ensuing ester **16** with $BF_3{\cdot}OEt_2$, provided lactam **17** very efficiently (94% yield; 20-mg scale). This reaction was

Scheme 1. Total Synthesis of (±)-Sessilifoliamide C (3) from Pyrrole 11[a]



[a]TEPA = triethylphosphonoacetate, MAA = methacrylic acid.

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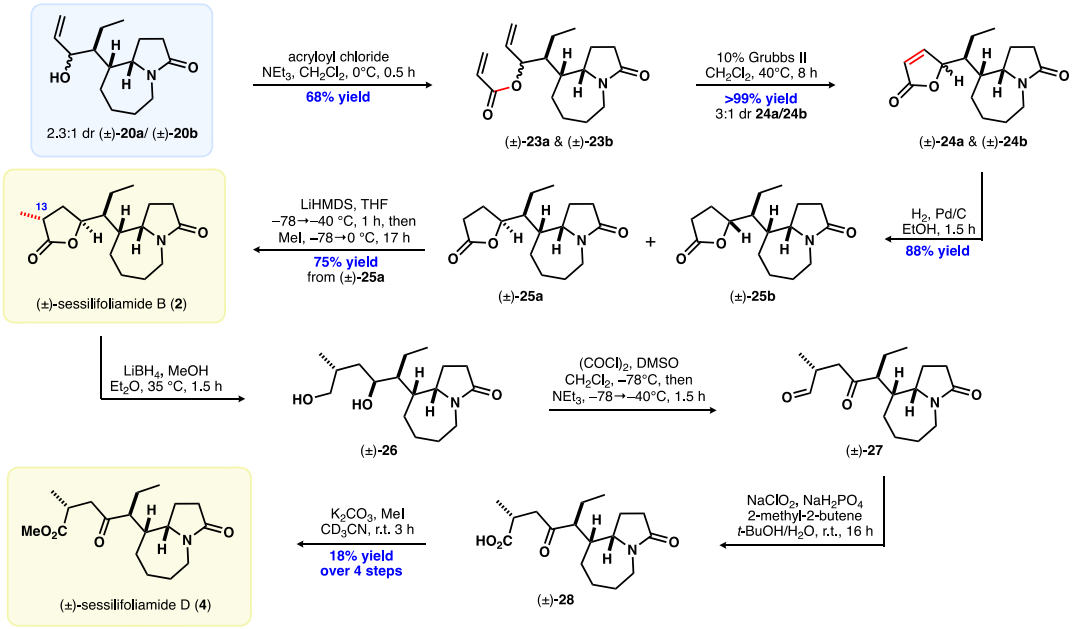
Scheme 2. Total Syntheses of (±)-Sessilifoliamides B (2) and D (4) from Key Synthetic Intermediate (±)-20



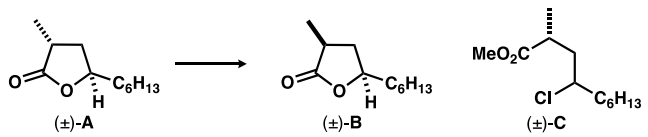
successfully scaled-up, and in this way, we prepared lactam **17** from pyrrole **15** in 81% yield over 2 steps on a gram scale, which illustrates the scalability of this DMP-controlled oxidation.[18,19] This method compares favorably to *m*-CPBA oxidations of polycyclic pyrroles to unsaturated γ-lactams employed in total syntheses of (±)-stemoamide (**6**) and sessilifoliamide A (**1**).[8c,20]

The palladium-catalyzed hydrogenation of diene **17** proceeded smoothly to furnish diastereomers **12** (5.7:1 ratio) quantitatively. By this approach, we successfully obtained bicyclic-lactams (±)-**12** on a gram scale in 41% yield over 6 steps. Having reached key intermediate **12a**, the ethyl ester analogue of lactam **10a** reported by Wipf and Hoye,[10] we based our end-game approach to sessilifoliamide C on their efficient route. Specifically, esters **12** were reduced to alcohols **18** with $LiBH_4$. Wipf and Hoye employed $LiBH_4$ (10 equiv) in THF over a two-day reaction time to achieve this. We observed that the reduction of esters **12** also proceeded very slowly under these conditions. However, by using $LiBH_4$ (5 equiv) in an Et_2O/methanol solvent mixture with mild heating (35 °C) over 4.5 h, chromatographically separable diastereomers **18** were obtained in 77% combined yield. The Swern oxidation of alcohol **18a**, followed by nucleophilic addition of vinylmagnesium bromide to ensuing aldehyde **19**, furnished vinyl alcohols **20** quantitatively over two steps. These substrates were then treated with methacryloyl chloride to give chromatographically inseparable methacrylate esters **21**. Finally, an RCM promoted by the Grubbs second generation catalyst furnished sessilifoliamide C (**3**) and its C-11 epimer (**22**) in excellent yield. We obtained sessilifoliamide C and its C-11 epimer in 24% yield from pyrrole **11** by this route. The NMR spectroscopic data obtained for sessilifoliamide C were consistent with equivalent data for the isolated natural product (see Supporting Information).[1]

After completing the synthesis of sessilifoliamide C (**3**) we turned our attention to preparing sessilifoliamide B (**2**). Because the palladium-catalyzed hydrogenation of sessilifoliamide C was shown to selectively deliver the C-13 epimer of sessilifoliamide B, rather than natural product **2**,[1] we opted to synthesize sessilifoliamide B via a late-stage stereoselective methylation of the lactone ring. To this end, vinyl alcohols **20** were treated with acryloyl chloride to furnish acrylate esters **23** (Scheme 2). The RCM and hydrogenation steps proceeded efficiently to provide lactones **25** which were partially separable by flash chromatography. α-Methylation of lactone **25a** was completed in 75% yield, thereby furnishing sessilifoliamide B (**2**). The NMR spectroscopic data obtained for compound **2** were consistent with equivalent data for the isolated natural product (see Supporting Information).[1]

In planning our approach to sessilifoliamide D (**4**) we wondered whether the target could be accessed via the nucleophilic opening (transesterification) of sessilifoliamide B (**2**) by methanol/methoxide followed by oxidation of the resulting hydroxy ester. To this end, we explored the viability of various conditions on model lactone **A**. We found that treatment with methoxide resulted in C-2 epimerization to afford **B**, rather than nucleophilic acyl substitution (Table 1, entry 1). Treatment of lactone **A** with catalytic DCl in methanol-d_4 (generated in situ from $SOCl_2$) did not yield the

Table 1. Attempted Transesterification of Model Lactone A



entry	reaction conditions	outcome[a]
1[b]	NaOMe, MeOH, rt, 48 h	1:2 **A**/**B**
2	$SOCl_2$, CD_3OD, 40 °C, 24 h	**A** + **C**
3	DMAP, CD_3OD, 40 °C, 24 h	no reaction
4	DMAP, CD_3OD, 65 °C, 24 h	no reaction
5	H_2SO_4, CD_3OD, 65 °C, 24 h	no reaction

[a]Reaction monitoring by ^1H NMR spectroscopy. [b]Reaction was monitored by TLC and analyzed by ^1H NMR spectroscopy after aqueous workup.

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desired hydroxy ester (entry 2). Instead, partial conversion to chloride **C** occurred. Attempts to effect DMAP and sulfuric acid catalyzed transesterifications (entries 3−5) also proved unsuccessful. Although these observations suggested that the transesterification of sessilifoliamide B (**2**) was not likely to deliver target **4**, we reacted substrate **2** with K_2CO_3 in methanol. This resulted in the epimerization at C-13 and the desired hydroxy-ester was not formed, which was consistent with our expectations following experiments using model system **A**.

Our above-mentioned observations dictated that the route to sessilifoliamide D (**4**) should proceed via 1,4-diol **26**, which could be accessed by the reduction of sessilifoliamide B (**2**) (Scheme 2). The reaction of lactone **2** with $LiBH_4$ proceeded smoothly to afford 1,4-diol **26**; however, the Swern oxidation of substrate **26** to ketoaldehyde **27** was inefficient.[21] This may have derived from the small reaction scale (9 mg of **26**). Nevertheless, the subsequent Pinnick oxidation of ketoaldehyde **27** and O-methylation of keto acid **26** with iodomethane proceeded without complication to furnish sessilifoliamide D (**4**) in 18% yield over 4 steps from sessilifoliamide B (**2**). The NMR spectroscopic data obtained for compound **4** were consistent with equivalent data for the isolated natural product (see Supporting Information).[1]

In summary, we have successfully completed the second total synthesis of sessilifoliamide C (**3**), and the first total syntheses of sessilifoliamides B (**2**) and D (**4**) via common intermediate **20** accessed from an inexpensive pyrrole substrate. Key bicyclic lactam core structure (±)-**12** was obtained on a gram scale via a Brønsted acid mediated intramolecular conjugate addition and the controlled oxidation of pyrrole **15** with DMP. Both of these lynchpins were high-yielding (≥80%). Sessilifoliamide C along with C-11 epimer was obtained in 24% yield over 11 steps while sessilifoliamides B and D were synthesized in 13 and 17 steps, respectively. Although the natural products that formed the basis of this study were prepared racemically, we anticipate that our approach could be modified to achieve enantioselective syntheses, for example, by employing the Evans oxazolidinone to facilitate the stereoselective ethylation of pyrrole **14**, or using this chiral auxiliary to facilitate the diastereoselective epimerization of lactam **17**.[22]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00895.

Additional experimental information and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(19) This is the first time that this DMP pyrrole oxidation protocol has been deployed in a total synthesis of a natural product.
(20) In ref 8c, the authors noted that low yields were obtained if commercially available *m*-CPBA was used as received. Lactam yields were improved (40−65%) by employing purified *m*-CPBA at −35 °C in DCE on <50 mg scales.
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