Total Syntheses of the C_{19} Diterpenoid Alkaloids (–)-Talatisamine, (–)-Liljestrandisine, and (–)-Liljestrandinine by a Fragment Coupling Approach

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The extracts of the *Aconitum* and *Delphinium* genera of plants have long been used in traditional medicine and as poisons for hunting and battle.[1] The diterpenoid alkaloids are a family of natural products associated with the toxicity of these flowering plants, and many of these compounds exhibit analgesic,[2] anti-inflammatory, antihypertensive, and antiarrhythmic[3] properties. (–)-Talatisamine (**1**, Figure 1a) is a representative aconitine-type C19 diterpenoid alkaloid (C19 DTA) that selectively blocks inwardly rectifying K^+ ion channels over Na^+ and Ca^{2+} ion channels in rat neurons,[4] and was found to attenuate neurocytotoxicity induced by β-amyloid oligomers.[5] Minor congeners, such as (–)-liljestrandisine (**2**) and (–)-liljestrandinine (**3**), which vary in the methylation and oxidation pattern, have also been isolated.[6]

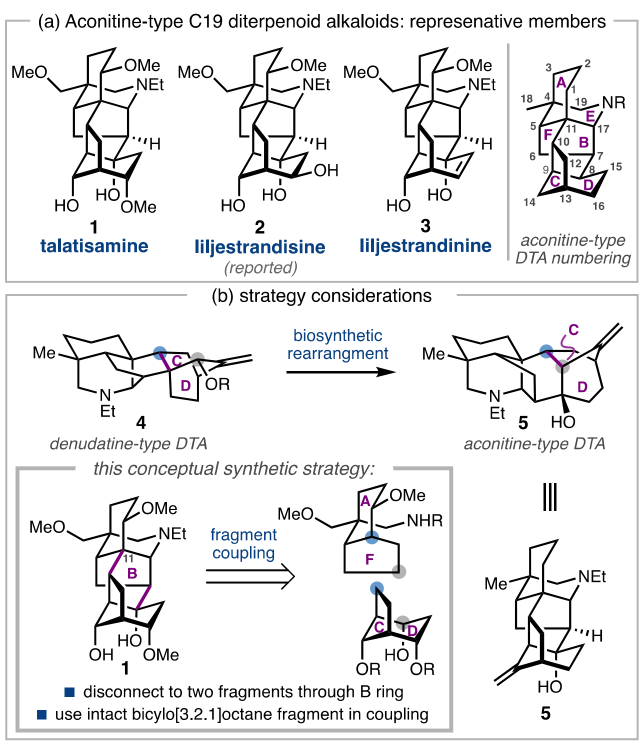


Figure 1. Representative members of the aconitine-type C19 diterpenoid alkaloids and synthetic strategy considerations.

Biosynthetically, the C19 DTAs arise via the *ent*-atisane cyclase pathway, in which the originally formed denudatine framework (**4**), containing a bicyclo[2.2.2]octane CD ring system, undergoes skeletal rearrangement to the corresponding [3.2.1] CD ring system (**5**) (Figure 1b).[7] The cationic rearrangements involved in the biosynthesis of these natural products have also played an important role in many of the total syntheses of the C19 DTAs, including the pioneering efforts in the 1970s by Wiesner and coworkers,[8] and more recent contributions by the Sarpong,[9] Fukuyama,[10] and Inoue labs.[11] In each of these approaches, the denudatine-type bicyclo[2.2.2]octane is first assembled by a Diels–Alder reaction, and then rearranged at a late stage to the aconitine-type skeleton. Beyond these bioinspired strategies, a number of other approaches to the C19 DTAs have been disclosed,[12] as well as an elegant synthesis by Gin and coworkers of the C18 norditerpenoid alkaloid neofinaconitine (not shown).[13]

As part of a larger program aimed at developing fragment coupling strategies to prepare structurally complex diterpenes,[14] we became interested in the C19 DTAs as synthetic targets. We envisioned that scission of **1** through the C10–C11 and C7–C8 bonds of the central B ring would disconnect the highly bridged hexacyclic framework into two fragments of similar size and complexity (Figure 1b, inset). In the forward direction, the key steps of synthesis would focus on joining the AF ring system with an intact CD bicyclo[3.2.1]octane; we recognized that this approach would hinge the development of an efficient method to forge the central C11 quaternary center. In this communication, we report the total syntheses of (–)-talatisamine (**1**), (–)-liljestrandisine (**2**), and (–)-liljestrandinine (**3**), which feature a 1,2-addition/semi-pinacol rearrangement as the key fragment coupling tactic. These efforts have also resulted in a correction to the original structure assignment of (–)-liljestrandisine (**2**).[6b]

Given the conceptual strategy outlined in Figure 1, we developed the retrosynthesis of **1** shown in Figure 2. We sought to simplify **1** to amine **6** by disconnection of the C17–N and C7–C8 bonds; in the forward sense, we envisioned use of an *N*-centered radical cascade to close the E and B rings in a single transformation. Amine **6** was expected to be accessible from the corresponding ketone, **7**, via a series of reductions and amination at C19. To join the AF and CD rings, we designed a two-step sequence involving 1) 1,2-addition of an organometallic reagent derived from alkenyl bromide **10** to epoxy ketone **9**, and 2) semi-pinacol rearrangement of **8**, in which the strain-release of the epoxide opening would serve as a thermodynamic driving force for formation of the hindered C11 quaternary center. Although the semi-pinacol rearrangement has been used in many total syntheses,[15] it is not typically employed as part of a fragment coupling strategy; we anticipated that this approach could highlight the utility of this overall two-step tactic for building polycyclic systems. Finally, epoxyketone **9** and alkenyl bromide **10** would be prepared from the simple starting materials cyclopent-2-en-1-one (**11**) and phenol (**12**), respectively. It was expected that this approach to (–)-**1** would also provide access to (–)-(**2**) and (–)-(**3**) through adjustments to the final sequence of reduction steps.

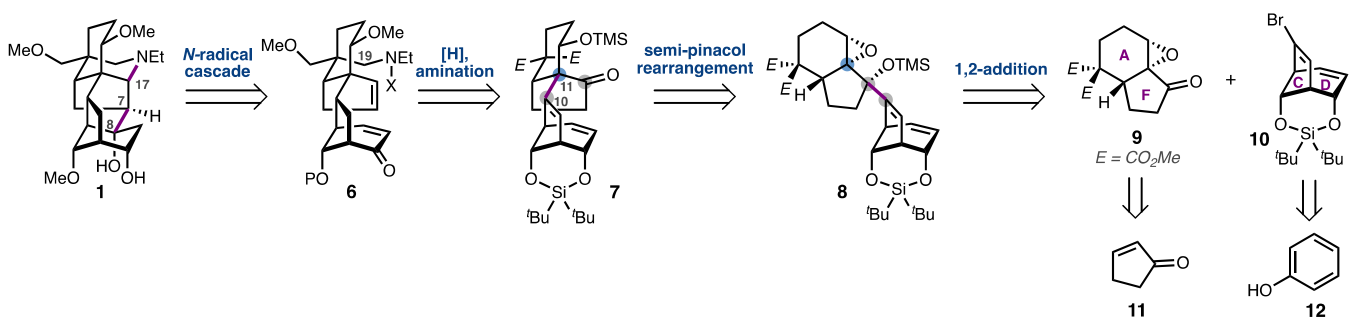
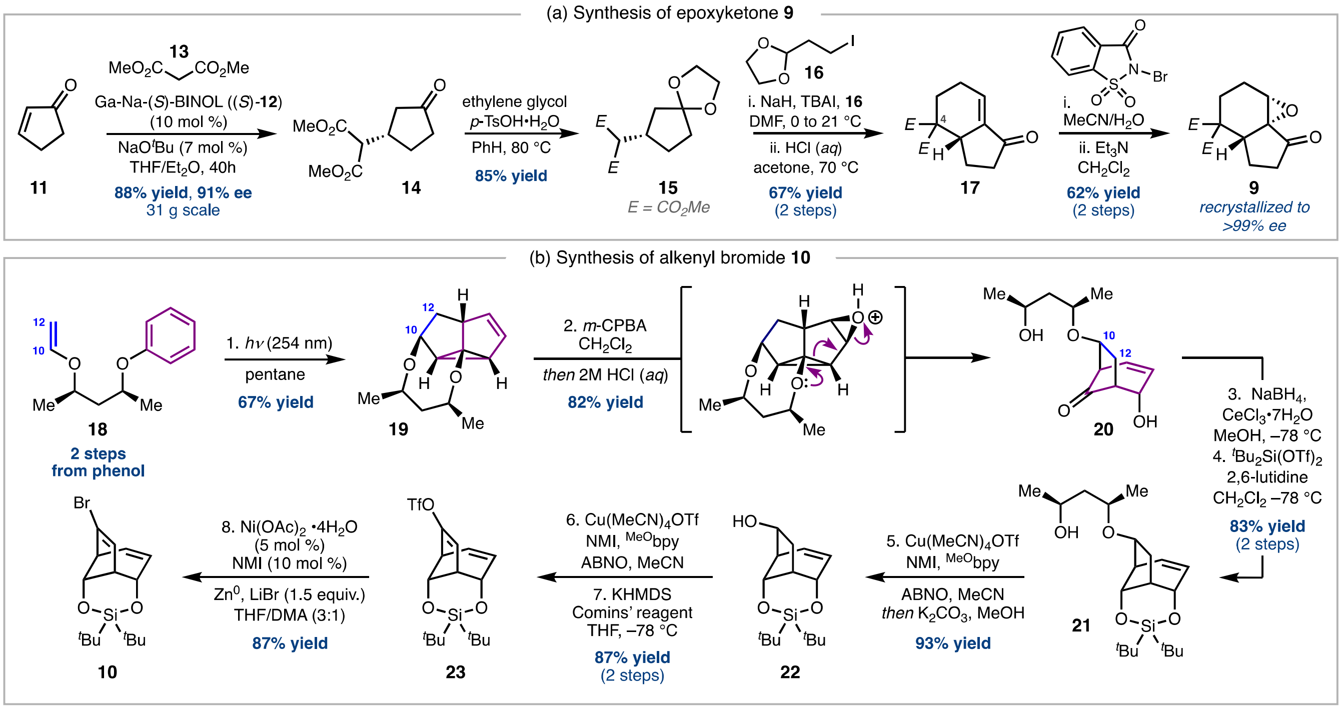


Figure 2. Retrosynthetic analysis of (–)-talatisamine (**1**).

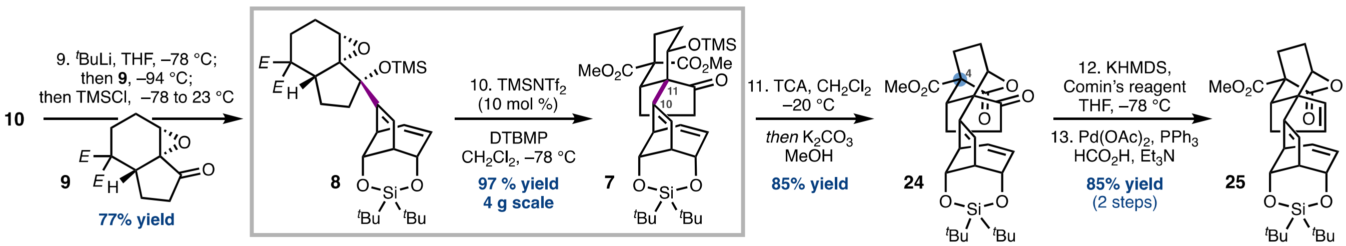
The synthesis of epoxy-ketone **9** began with the asymmetric Michael addition of dimethyl malonate (**13**) to **11** using the chiral gallium–sodium–BINOL catalyst ((*S*)-**12**) developed by Shibasaki and coworkers,[16] which furnished cyclopentanone **14** in 88% yield and 91% enantiomeric excess (ee) (Scheme 1a). The ketone of **14** was protected as the dioxolane to give **15**, which was alkylated with **16** and subjected to HCl in refluxing acetone to yield hydrindenone **17** in 67% yield over two steps. The required epoxide was accessed by first converting **17** to the bromohydrin, which was isolated as a single diastereomer after trituration.[17] Treatment with triethylamine followed by recrystallization furnished epoxyketone **9** in 62% yield (2 steps) and >99% ee.



Scheme 1. Enantioselective synthesis of epoxyketone **9** and alkenyl bromide **10**. Reagent abbreviations: *m*-CPBA–*meta*-chloroperbenzoic acid; NMI–*N*-methylimidazole; ABNO–9-azabicyclo[3.3.1]nonane *N*-oxyl radical; ^{MeO}bpy–4,4'-dimethoxy-2-2'-bipyridine.

The synthesis of the bicyclo[3.2.1]octadiene **10** commenced with a diastereoselective intramolecular *meta*-photocycloaddition of aryl ether **18** following the protocol reported by Sugimura (Scheme 1b).[18] Epoxidation of **19** and treatment with HCl resulted in Grob-type fragmentation to afford **20**. Luche reduction of **20** afforded the diaxial 1,3-diol, which was protected as a siliconide (**21**). The chiral auxiliary was cleaved by oxidation of the secondary alcohol under conditions reported by Stahl and coworkers[19] followed by addition of K_2CO_3 and methanol to liberate alcohol **22**. Upon oxidation to the ketone and conversion to enol triflate **23**, alkenyl bromide **10** was generated using a Ni-catalyzed enol-triflate halogenation developed in our laboratory.[20]

Having prepared **9** and **10**, we investigated the key fragment coupling step (Scheme 2). To this end, alkenyl bromide **10** was submitted to lithium-halogen exchange and the corresponding alkenyllithium was added to epoxyketone **9** at –94 °C to give the 1,2-addition product which, after quenching with TMSCl, was isolated as silyl ether **8** in 77% yield as a single diastereomer. To our delight, treatment of **8** with catalytic TMSNTf$_2$ (10 mol %) at –78 °C smoothly effected the desired semi-pinacol rearrangement. Under these conditions, ketone **7** is isolated in 97% yield on 4g scale. This remarkable two-step process forges the key C10–C11 bond and highlights the power of the 1,2-addition/ semi-pinacol rearrangement as a fragment coupling tactic for complex polycycles. Deprotection of the TMS-ether enabled cyclization to form the strained lactone **24**, thereby differentiating the two esters at C4. Conversion of the ketone to the enol triflate and Pd-catalyzed reduction afforded olefin **25** in excellent yield.

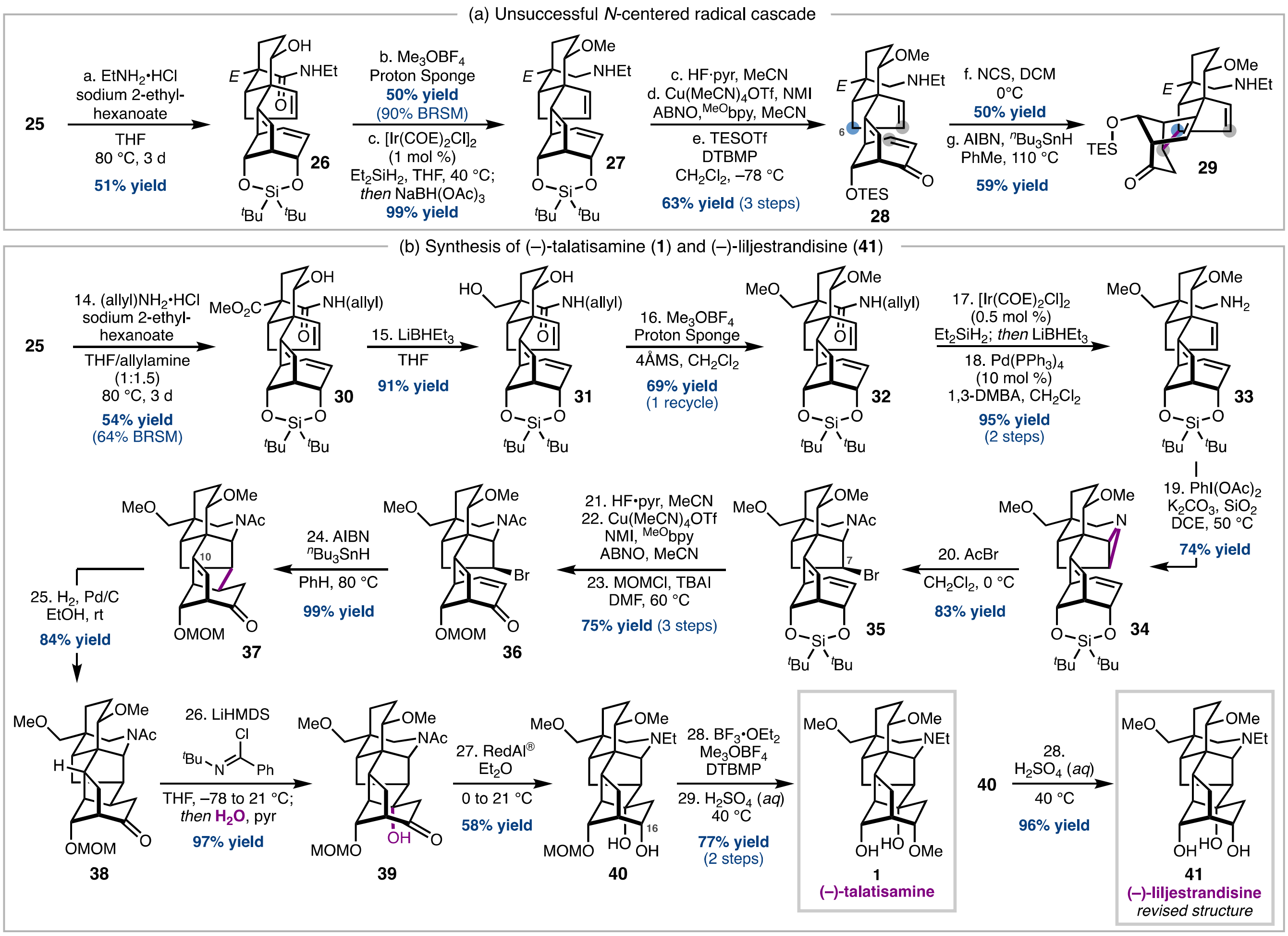


Scheme 2. Synthesis of lactone **25** using a 1,2-addition/semi-pinacol rearrangement as the key fragment coupling tactic. Reagent abbreviations: TMSCl–trimethylsilyl chloride; TMSNTf$_2$–*N*-(trimethylsilyl)bis(trifluoroethanesulfonyl)imide; DTBMP–2,6-di-*tert*-butyl-4-methylpyridine; TCA–trichloroacetic acid; KHMDS–potassium bis(trimethylsilyl)amide.

At this stage, we turned our attention to formation of the E and B rings by the proposed *N*-centered radical cascade (Scheme 3a). Access to the aminyl radical precursor required selective aminolysis of lactone **25** with ethylamine to give amide **26**. The secondary alcohol of **26** was methylated with trimethyloxonium tetrafluoroborate (Me_3OBF_4). Selective reduction of the C19-amide to the imine was achieved using the Ir-catalyzed hydrosilylation developed by Brookhart, and further reduction with $NaBH(OAc)_3$ afforded amine **27** in excellent yield.[21] A three step sequence involving desilylation, chemoselective oxidation of the allylic alcohol, and protection of the remaining secondary alcohol as the triethylsilyl ether gave CD enone **28**. Finally, treatment of **28** with *N*-chlorosuccinimide furnished the corresponding *N*-chloroamine (structure not shown). Unfortunately, efforts to effect the *N*-centered radical cascade under a number of conditions, including ^{n}Bu$_3$SnH/AIBN,[22] failed to give the desired product. Instead, under these conditions, the major product was **29**, presumably resulting from a 1,5-hydrogen atom transfer at C6 followed by 1,4-addition to the enone.

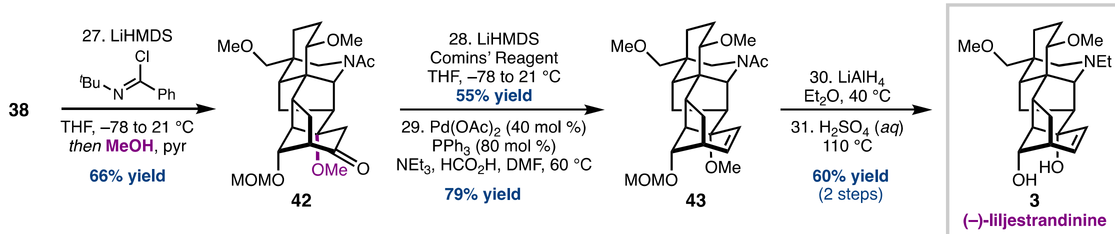
Having encountered challenges in forming the B and E rings through a cascade reaction, we pursued formation of the C–N and C–C bonds in a stepwise approach (Scheme 3b). To this end, aminolysis of lactone **25** with *N*-allylamine furnished amide **30** in 54% yield (64% BRSM). Reduction of the methyl ester followed by bis-methylation with Me_3OBF_4 delivered **32**. The C19 amide was reduced to the amine using conditions analogous to those employed en route to **27**; in this system, the Ir conditions proved uniquely effective at reducing the amide without also reducing the *N*-allyl group. The *N*-allyl substituent was cleaved under Pd-catalyzed conditions to give **33**.[23] Cyclization to form the E-ring piperidine was achieved by intramolecular aziridination,[12k] providing **34** in 74% yield. Treatment of aziridine **34** with acetyl bromide delivered alkyl bromide **35** in 83% yield. Notably, this transformation installed the C7 radical precursor and also introduced the two carbons of the *N*-ethyl substituent in the form of an acetamide. In analogy to **27**, siliconide **35** was elaborated to **36** by desilylation, oxidation, and MOM-protection of the C14 alcohol. We were pleased to find that heating **36** with $^{n}Bu_3SnH$ and AIBN resulted in the desired radical cyclization,[13] closing the B ring and delivering hexacyclic ketone **37** in 99% yield.

To complete the syntheses of (–)-**1** and (–)-**2**, hydrogenation of the strained C10–C12 alkene was followed by Mukaiyama dehydrogenation of the C16 ketone. Presumably, the strained bridgehead enone that initially forms undergoes oxy-conjugate addition upon addition of water and pyridine.[13,24] Treatment of **39** with Red-Al® reduced the acetamide to the *N*-ethylamine and the ketone to the alcohol, delivering **40** with good selectivity for the axial diastereomer. Selective methylation of the C16 alcohol of **40** followed by MOM deprotection afforded (–)-talatisamine ((–)-**1**) in 77% yield over the final two steps. Alternatively, treatment of **40** directly with aqueous H_2SO_4 gave triol **41**, and the ^{1}H and ^{13}C NMR data for which were consistent with that reported for (–)-liljestrandisine. Indeed, when the equatorial C16 epimer of **40** (not shown) was elaborated to compound **2** (Figure 1)—the originally proposed structure for (–)-liljestrandisine[6b]—the ^{1}H and ^{13}C NMR did not match the literature data. Based on this synthetic work, we propose that the structure of (–)-liljestrandisine should be revised to **41**.



Scheme 3. (a) Attempted *N*-centered radical cascade approach to (–)-**1**. (b) Completion of the synthesis of (–)-talatisamine (**1**) and structural revision of (–)-liljestrandisine (**43**). Reagent abbreviations: Proton Sponge®–1-8-bis(dimethylamino)naphthalene; NMI–*N*-methylimidazole; ABNO–9-azabicyclo[3.3.1]nonane *N*-oxyl radical; ^{MeO}bpy–4,4'-dimethoxy-2-2'-bipyridine; TESOTf–Triethylsilyl trifluoromethanesulfonate; DTBMP–2,6-di-*tert*-butyl-4-methylpyridine; NCS–*N*-chlorosuccinimide; AIBN–2,2'-azobis(2-methylpropionitrile); 1,3-DMBA–1,3-dimethylbarbituric acid; MOMCl–chloromethyl methyl ether; TBAI–tetrabutylammonium iodide; LiHMDS–Lithium bis(trimethylsilyl)amide; pyr–pyridine; RedAl®–sodium bis(2-methoxyethoxy)aluminum hydride.

The related target (–)-liljestrandinine (**3**) could be prepared from **38** by a slightly modified sequence. Dehydrogenation of **38** followed by addition of methanol and pyridine delivered C8 methyl ether **42** in 66% yield (Scheme 4). Conversion of ketone **42** to the enol triflate followed by Pd-catalyzed reduction gave alkene **43**. Amide reduction with lithium aluminum hydride followed by MOM deprotection and S_N1 hydrolysis of the C8 methoxy group delivered (–)-**3**.



Scheme 4. Completion of the synthesis of (–)-liljestrandinine (**3**). Reagent abbreviations: LiHMDS–Lithium bis(trimethylsilyl)amide.

In conclusion, the C19 DTAs (–)-talatisamine, (–)-liljestrandisine, and (–)-liljestrandinine have been prepared in 31, 30, and 33 steps, respectively, from phenol (**12**). Our synthetic approach leverages a 1,2-addition/semi-pinacol rearrangement sequence as a powerful tactic for the coupling of complex ring-containing fragments. Although efforts to use an *N*-centered radical cascade to simultaneously form the E and B rings were unsuccessful, the general bond constructions could be executed in a stepwise fashion by way of an intramolecular aziridination and subsequent radical cyclization. These studies highlight the 6-*exo*-trig cyclization of *N*-centered radicals as a prime area for future reaction development. Efforts to apply similar fragment coupling strategies in combination with radical cascade reactions to other DTAs are ongoing in our laboratory.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data (^{1}H and ^{13}C NMR, HRMS, FTIR) for all new compounds (pdf).

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