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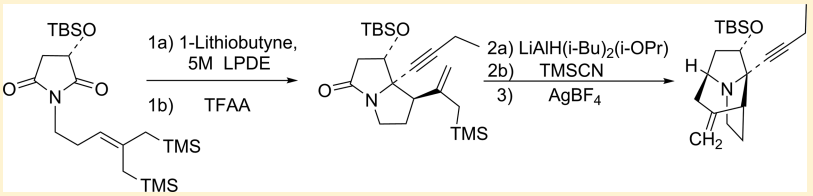
Divergent Stereocontrolled Synthesis of the Enantiopure Tetracyclic Cores of Asparagamine A and Stemofoline via an Intramolecular 2-Propylidine-1,3-(bis)silane Bicyclization

Bryon K. Anderson and Tom Livinghouse*

Department of Chemistry and Biochemistry, Montana State University, Bozeman, Montana 59717, United States

Supporting Information

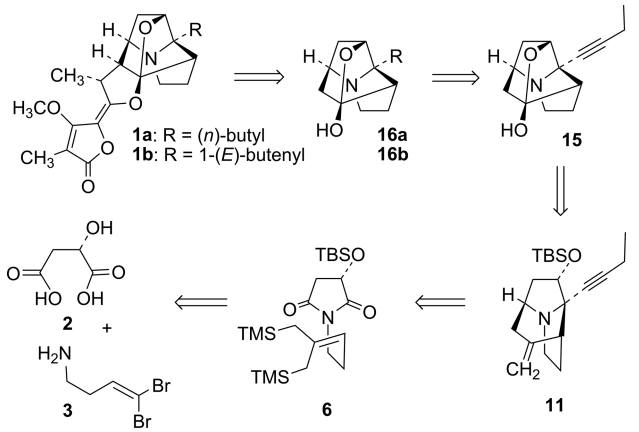


ABSTRACT: A concise and highly diastereoselective synthesis of the polyfused tetracyclic cores of the *Stemona* alkaloids asparagamine A and stemofoline that relies on a 2-propylidine-1,3-(bis)silane bicyclization onto a enantiodefined pyrrolidine 2,5-di(cation) equivalent derived from L-malic acid is reported. A crucial feature of this divergent synthetic approach involves the solvolysis of a transient and highly labile tertiary-propargylic hydroxylactam trifluoroacetate in the strongly ionizing medium 5 M $LiClO_4/Et_2O$. The acyliminium ion generated in this manner undergoes stereospecific interception by the aforementioned (bis)silane nucleophile.

INTRODUCTION

In 1970, Irie and co-workers isolated a unique alkaloid, stemofoline (**1a**), from the plant *Stemona japonica* and acquired structure information from X-ray crystallography examination.[1] The closely related *Stemona* alkaloid, asparagamine A (**1b**), was isolated from the roots of *Asparagus racemosus* and completely characterized in 1994.[2] Biological studies on these closely related alkaloids have revealed notable insecticidal properties when administered orally to the larvae of various crop pests, such as the diamondback moth.[3a−c] Additionally, asparagamine A was found to possess antitumor and antioxytocin biological activity in vitro.[4] Subsequent to their discovery, **1a** and **1b** have been the topic of several synthetic endeavors, with three culminating in completed syntheses[5a−c] and four leading to tetracyclic core substructures present in these alkaloids.[6a−d] We have previously demonstrated the utility of 2-propylidene-1,3-bis(silane)-terminated cyclizations involving iminium cations for the stereocontrolled synthesis of isotropanes, including a simple azatricycle similar to that found in **1a** and **1b**.[7] In this paper, we report the application of this protocol to a concise and divergent assembly of the enantiopure tetracyclic cores found in *both* stemofoline (**1a**) and asparagamine A (**1b**). We envisaged that the saturated and unsaturated core elements **16a** and **16b**, respectively, could be transformed into more advanced intermediates via alkylation of the corresponding nonbridgehead ketone enolates in a manner reminiscent of previous syntheses.[5a,b] Intermediates **16a** and **16b**, in turn, could converge on the acetylenic lactol **15** by complete or partial reduction, respectively, with the latter mapping nicely onto the enyne **11** by way of inversion of the oxygen-bearing stereocenter and oxidative alkene cleavage. Enyne **11** was expected to be synthetically available by a sequential 2-propylidene-1,3-bis(silane) bicyclization onto an enantiodefined pyrrolidine 2,5-di(cation) equivalent derived from imide **6**, which would ultimately emanate from amine **3** and L-malic acid (**2**) (Scheme 1).

Scheme 1. Retrosynthetic Strategy



RESULTS AND DISCUSSION

The synthetic plan outlined above was implemented in the following manner. Sequential treatment of anhydride **4**, which is conveniently prepared from L-malic acid (**2**), with amine **3**[8] followed by AcCl and subsequent acetate cleavage (HCl−EtOH,

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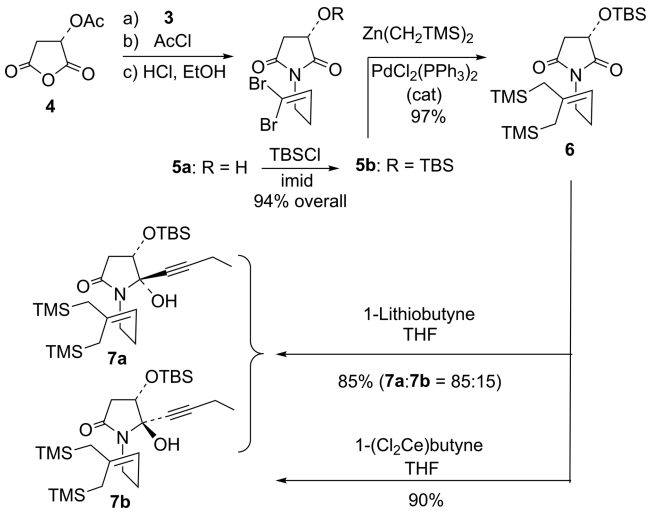
generated in situ from AcCl), in an adaptation of the method of Chamberlin,[9] furnished imide **5a** and ultimately **5b** [TBSCl, imidazole (94% over four steps)]. Subsequent exposure of **5b** to a preformed THF solution of $Zn(CH_2TMS)_2$ in the presence of $PdCl_2(PPh_3)_2$ (7 mol %), led to efficient cross-coupling to deliver bis(silane) **6** in 97% isolated yield (Scheme 2).[8] Our

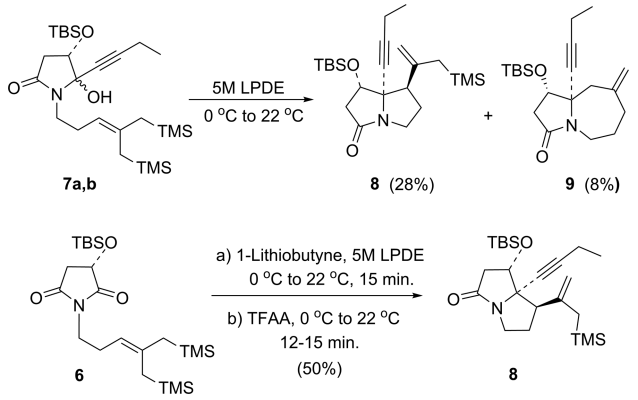
Scheme 2. Synthesis of Hydroxylactams 7a and 7b



original plans entailed the treatment of **6** with 1-lithiobutyne to give the corresponding hydroxylactams **7a** and/or **7b** that would then be subjected to an "acyliminium ion–allylsilane" cyclization protocol.[10a–d] Accordingly, addition of **6** to 1-lithiobutyne (3 equiv) in THF (−78 °C → −30 °C) provided **7a** admixed with **7b** (**7a**/**7b** = 85:15), which were readily separated by chromatography, in 85% combined yield. The chemoselectivity of addition is in accord with the documented propensity of preferential nucleophilic attack at the "inductively activated" carbonyl function in related cyclic imides.[7,11] Interestingly, treatment of **6** with the corresponding dichloroceriumacetylide (3 equiv, THF, −78 °C → −30 °C) gave **7b** as the predominant product (90%, NMR). Although we have yet to firmly establish that the latter is a result of kinetic control, it is noteworthy that treatment of **7b** with *n*-BuLi (1 equiv, −78 °C → −30 °C) led to its equilibration to a mixture of *both* diastereomers (**7a**:**7b** = 35:65). In addition, subjection of **7a** to dichloroceriumacetylide (1 equiv, THF, −78 °C → 0 °C) followed by quenching with saturated aqueous NH_4Cl resulted in no equilibration. The latter result is consistent with the enhanced rigidity expected for a Ce–O bond compared to coordination by simple alkali cation.

Cyclization Studies. Attempts to effect the desilylative cyclization of the hydroxylactams **7a** and **7b** under a wide variety of conventional ionizing conditions involving Brønsted or Lewis acids led, not surprisingly, to extensive protodesilylation of the 2-propylidene-1,3-bis(silane) assembly present in these precursors. In a series of seminal contributions, Grieco and co-workers have shown that anhydrous 5 M $LiClO_4$ in Et_2O (5 M LPDE) is a remarkable medium for accelerating organic reactions.[12a–e] We were therefore encouraged that simple dissolution of **7a**,**b** in 5 M $LiClO_4$–Et_2O provided **8** (28% isolated yield) [admixed with the azabicyclic byproduct **9** (8%) plus several unidentified products]. The observed formation of 1-azabicyclo[5.3.0]decane **9** was believed to arise from an initial monoprotodesilylation event followed by a classical acyliminium ion cyclization of the resultant pendant allylsilane. Efforts to buffer the reaction medium with various acid scavengers or molecular sieves led to no improvement in cyclization efficiency or significant suppression of any reaction. It is also worthy of note that resubjection of **8** to 5 M $LiClO_4$–Et_2O did *not* result in its protodesilylation. In addition, 2-[(trimethylsilyl)methyl]-1-(trimethylsilyl)-2-propene[13] proved inert to this reaction medium, thereby suggesting that the hydroxylic proton present in the precyclization substrates **7a**,**b** was the most likely source of the problem. To explicitly avoid this possibility, *it was ultimately found that treatment of* **6** *with 1-lithiobutyne (1.2 equiv) in 5 M* $LiClO_4$–Et_2O *(0 °C → rt) followed by alkoxide interception with TFAA gave* **8** *directly and without competing protodesilylation in 50% yield as a single diastereomer* (Scheme 3).

Scheme 3. Acyliminium Ion–Allylsilane Cyclization Protocol



Conclusive evidence for the relative stereochemistry of pyrrolizidine **8** was ultimately obtained by the successful realization of the subsequent iminium ion–allylsilane cyclization (vide infra). The observed stereochemistry of ring closure is also in accord with the prior results of Speckamp and Hiemstra. By virtue of substrate-directed stereocontrol, the 2-(propylidine)-1,3-bis(silane) terminator is directed in an anti orientation relative to the sterically demanding TBSO group. The stereospecificity of the terminating allylsilane can be rationalized by stereoelectronic factors inherent in the intermediate π-complex configurations.[14] Specifically, the relative stability of the two relevant π-complex configurations can be accessed by comparing the steric interactions expected in the competing chair- or boatlike transition states. In this context, the chairlike conformation would be preferred due to minimization of eclipsing interactions that would develop in the boatlike alternative (Figure 1).[15]

Elaboration of the Tetracyclic Core. Our attention was now directed toward the closure of the azatricyclic core

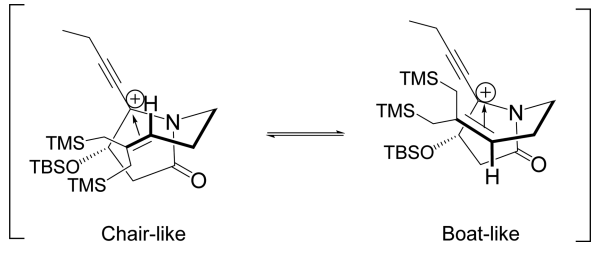


Figure 1. Transition-state analysis.

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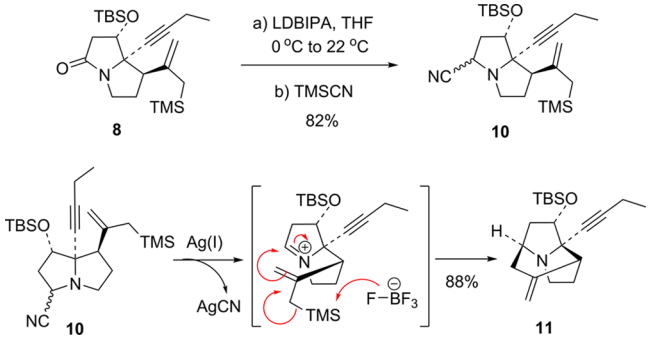
common to stemofoline and asparagamine A via an iminium ion−allylsilane cyclization. Apropos of this strategy, the seminal investigations of Stork regarding the utility of α-cyanoamines as iminium ion equivalents were considered most relevant.[16] Recent examples that have been reported for the conversion of lactams to the corresponding α-cyanoamines include preliminary reduction using $LiAlH(OEt)_3$ followed by KCN/AcOH[17] or *n*-BuLi·DIBAL-H followed by TMSCN.[18] In our hands, the use of the former reducing reagent proved most unsatisfactory, while *n*-BuLi·DIBAL-H exhibited some promise. Recently, it has been shown that a wide variety of tertiary amides can be partially reduced in near-quantitative yields (89−99%) using alkoxy variants of the DIBAL−ate complexes.[19] This proved to be the case in the present instance wherein partial reduction of **8** with $LiAlH(i\text{-}Bu)_2(i\text{-}OPr)$ (LDBIPA)[19] followed by immediate treatment with TMSCN provided cyanoamines **10** in 82% isolated yield. It should be noted that preliminary cyanoamine generation was a prerequisite for successful closure to **11**. Subsequent exposure of **10** to $AgBF_4$ (1.1 equiv, THF, 22 °C) induced the desired iminium ion−allylsilane cyclization to furnish azatricycle **11** in excellent (88%) yield (Scheme 4).[20]

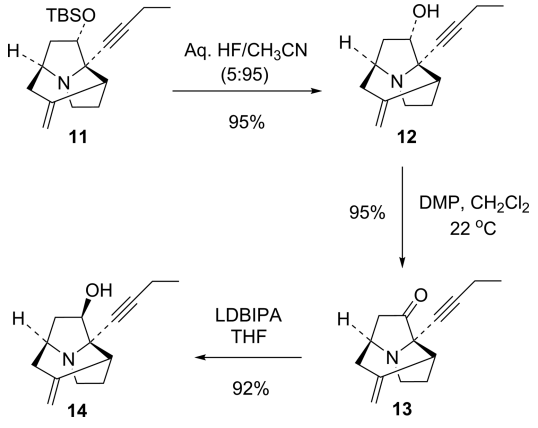
Scheme 4. Allylsilane Termination To Form the Azatricyclodecane Core



The construction of the alkyne-bearing azatetracyclic core element was achieved in the following manner. Stereochemical inversion at the oxygen-bearing center was readily accomplished by sequential hydroxyl deprotection (HF, MeCN), oxidation (Dess−Martin periodinane), and stereospecific carbonyl reduction (LDBIPA)[19] to furnish the azatricyclic intermediate **14** in 83% overall yield (Scheme 5).

Firm evidence for the desired inversion of hydroxyl configuration was revealed in the ^1H NMR spectrum wherein the doublet-of-doublets signal produced by the diastereotopic hydrogen opposite to the inverted alcohol was shifted downfield in comparison to the corresponding *exo* isomer, resulting from the disposition of this diastereotopic hydrogen in the deshielding zone of the alkyne.[21] Subsequent single-crystal X-ray analysis confirmed this structural assignment (Figure 2 and Supporting Information).

Scheme 5. Stereochemical Modification Sequence



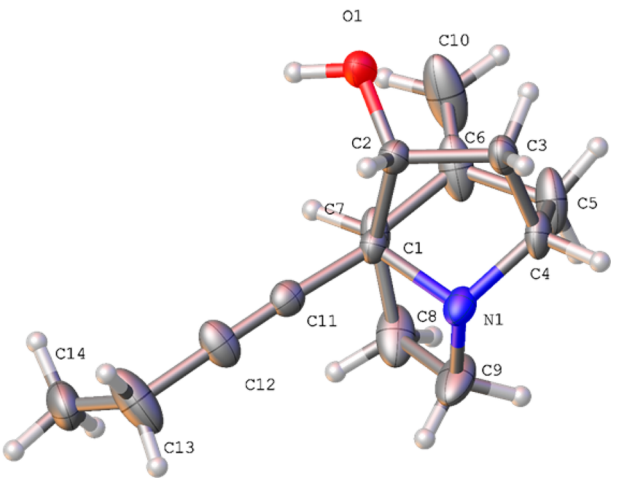
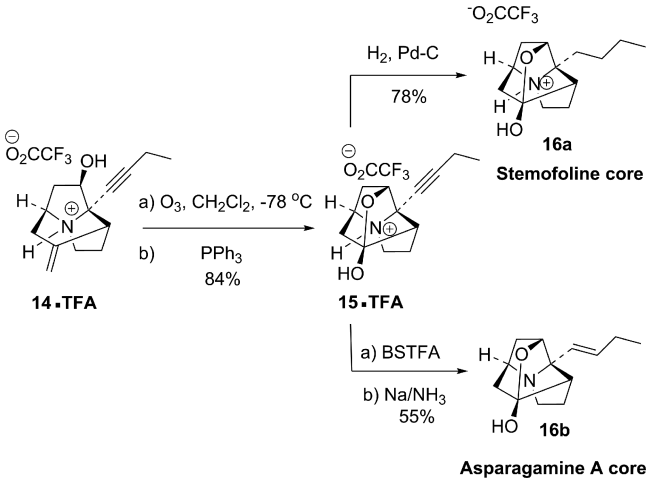


Figure 2. X-ray crystal structure of azatricycle **14** (ORTEP ellipsoids are depicted at the 50% level).

It should be noted that the alternative approach involving a Mitsunobu inversion was not attempted due to the secondary neopentyl-like site of prospective nucleophilic attack.

Oxidative cleavage of the pendant methylene substituent present in **14** was most expeditiously achieved by selective ozonolysis of the corresponding TFA salt **14**·TFA (−78 °C) followed by reductive workup using Ph_3P, to afford the hemiketal salt **15**·TFA in excellent (84%) yield. Subjection of **15**·TFA to hydrogenation (H_2, Pd/C, cat.) efficiently provided the tetracyclic stemofoline core element **16a**·TFA in 78% isolated yield. Alternatively, *O*-silylation of **15**·TFA (*N*,*O*-bis(trimethylsilyl)trifluoroacetamide, BSTFA) followed by direct reduction (Na/NH_3) secured the asparagamine A based lactol **16b** as the free amine in 55% yield (Scheme 6). Direct reduction of **15**·**TFA** resulted in inferior yields of **16b**.

Scheme 6. Completion of the Azatricyclic Cores



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CONCLUSION

In conclusion, a stereocontrolled intramolecular 2-propylidine-1,3-(bis)silane cyclization cascade has been successfully utilized in a divergent synthetic route to the enantiopure tetracyclic core elements of stemofoline (**1a**) and asparagamine A (**1b**). Among the most salient features of the present synthetic strategy are the ability of the 2-propylidine-1,3-(bis)silane binary nucleophile to engage an incipient tertiary propargylic acyliminium ion with excellent stereoselectivity and without concomitant protodesilylation. A subsequent intramolecular allylsilane−iminium ion cyclization involving an α-cyanoamine completed the construction of the skeletal core common to the aforementioned alkaloids. The chiral 2,5-pyrrolidine dication equivalent that serves as a template for these transformations is conveniently prepared from L-malic acid (**2**).

EXPERIMENTAL SECTION

Materials and Methods. Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl under nitrogen. Dichloromethane and triethylamine were distilled from calcium hydride under nitrogen. Dimethylformamide was distilled from calcium hydride under reduced pressure. Isopropyl alcohol was dried by distillation from calcium hydride after preliminary drying from KOH pellets. $ZnCl_2$ was fused under vacuum using a Bunsen burner prior to use. TBSCl was purified by distillation, and imidazole was recrystallized from 1:1 heptane−toluene. $LiClO_4$ and $AgBF_4$ were dried under reduced pressure (0.001 mmHg, 120 °C, 24 h) and handled in a drybox. All other materials were used as received from commercial sources. Thin-layer chromatography (TLC) employed 0.25 mm glass silica gel plates with UV indicator and visualized with UV light (254 nm), potassium permanganate, or 2,4-dinitrophenylhydrazine staining. Flash chromatographic columns were packed with silica gel 60 as a slurry in the initial elution solvent.

Preparative Procedures. *3-Phthalimidopropionaldehyde.* The compound was prepared following an analogous procedure described by Leete.[22] An oven-dried 250 mL round-bottom flask equipped with a magnetic stirring bar, condenser, and nitrogen inlet was charged with phthalimide (15.9 g, 108 mmol, 1.00 equiv) and acrolein (6.67 mL, 119 mmol, 1.10 equiv) suspended in ethyl acetate (64 mL). The suspension was allowed to stir for 5 min at 65 °C prior to the addition of Triton B (40% solution of benzyltrimethylammonium hydroxide in MeOH, 362 μL, 2.17 mmol, 0.020 equiv). Reaction progress was monitored by TLC (25% ethyl acetate in hexanes, 2,4-DNP stain). After 15 min, or until the reaction mixture became heterogeneous, solvents were removed, and the resulting off-white solid was triturated (30 mL ethyl ether) and filtered to afford the product as a white solid (20.12 g, 91%). The product was used without further purification: ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.83 (s, 1H), 7.86 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.05 (t, *J* = 7.0 Hz, 2H), 2.89 (td, *J* = 7.0, 1.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.6, 168.2, 134.3, 132.2, 123.6, 42.6, 31.9; IR (film) 2946, 2850, 2739, 2332, 1767, 1708, 1612, 1464, 1442, 1398, 1139, 1028, 891, 714, cm^{-1}.

1,1-Dibromo-4-phthalimido-1-butene. The compound was prepared following analogous procedures described by Corey[23] and Kercher.[24] An oven-dried 100 mL round-bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with carbon tetrabromide (3.264 g, 9.842 mmol, 2 equiv) and zinc dust (0.6430 g, 9.842 mmol, 2.0 equiv) dissolved in dichloromethane (17 mL) freshly distilled from calcium hydride. The gray reaction mixture was cooled to 0 °C prior to the dropwise addition of triphenylphosphine (2.581 g, 9.842 mmol, 2.0 equiv) in dichloromethane (3 mL) over 30 min. After the resulting olive-green mixture was stirred for an additional 10 min at 0 °C, 3-phthalimidopropionaldehyde (1.0 g, 4.9 mmol, 1 equiv) dissolved in dichloromethane (7 mL) was added over 30 min via syringe. The dark burgundy mixture was stirred for 21.5 h at room temperature and monitored by TLC (25% ethyl acetate in hexanes). The reaction mixture was then diluted with hexanes (25 mL) and vigorously stirred for 5 min. The supernatant was decanted and filtered over Celite to provide a crude off-white solid. The solid precipitate from the reaction was reworked four times by redissolving in dichloromethane and diluting with hexanes (4 × 25 mL). The crude product was then redissolved in CH_2Cl_2 (40 mL) and treated with oxalyl chloride (0.85 mL, 9.8 mmol, 2.0 equiv) at 0 °C with stirring.[25] After 1 h at 22 °C, the reaction mixture was quenched by slow addition of saturated $NaHCO_3$ (40 mL) and diluted with hexanes (30 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to provide the title compound as a white solid (1.07 g, 61%): mp = 115−117 °C; ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.87 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.1 Hz, 2H), 6.46 (t, *J* = 7.3 Hz, 1H), 3.81 (t, *J* = 6.9 Hz, 2H), 2.51 (q, *J* = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 134.5, 134.1, 132.0, 123.4, 91.7, 35.6, 32.4; IR (film) 3101, 3027, 2942, 2362, 2337, 1767, 1697, 1396, 1364, 1242, 1132, 1043, 988, 873, 747, 718, cm^{-1}.

*1,1-Dibromo-4-amino-1-butene (**3**).* An oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar, condenser, and nitrogen inlet was charged with 1,1-dibromo-4-phthalimido-1-butene (4.119 g, 11.47 mmol, 1.0 equiv) in degassed absolute ethanol (33 mL). Hydrazine monohydrate (1.21 mL, 24.1 mmol, 2.10 equiv) was added all at once with stirring at 60 °C and held at that temperature for 20 h or until deemed complete by GC. The phthalhydrazide byproduct was triturated (30 mL of ethyl ether) and filtered. The ethanol-containing filtrate was concentrated by azeotropic distillation (benzene) to afford the compound as a yellow oil, which could be used without further purification or distilled from calcium hydride (63−65 °C, 1.3 mmHg) to provide a colorless liquid (1.83 g, 70%): ^{1}H NMR (300 MHz, chloroform-*d*) δ 6.38 (t, *J* = 7.2 Hz, 1H), 2.73 (t, *J* = 6.8 Hz, 2H), 2.17 (q, *J* = 6.8 Hz, 2H), 1.23 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 90.3, 40.4, 37.3. IR (film) 3438, 3312, 3017, 2861, 2924, 2340, 1563, 1475, 1430, 1383, 1317, 810 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_4H_7Br_2N$ (M + *n*H) 227.9018, found 227.9024.

*(3S)-2,5-Dioxotetrahydrofuran-3-yl acetate (**4**).* Compound **4** was prepared following analogous procedures described by Chamberlin[9] and Lee.[11] An oven-dried 200 mL round-bottom flask equipped with a magnetic stirring bar, condenser, and nitrogen inlet was charged with L-malic acid **2** (6.70 g, 43.9 mmol) and acetyl chloride (83.84 mL). The reaction mixture was allowed to stir at reflux for 18 h. Evaporation of solvent under reduced pressure afforded a clear viscous residue, which was triturated with toluene and dried by codistillation to provide the title compound as an off-white sold. The crude anhydride was recrystallized from benzene to furnish the pure product as a white solid (7.74 g, 98%): mp 56−59 °C; $[\alpha]^{20}_D$ = −23.2 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.54 (dd, J = 9.6, 6.4 Hz, 1H), 3.40 (dd, J = 18.9, 9.6 Hz, 1H), 3.04 (dd, J = 18.9, 6.4 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 167.8, 166.4, 67.7, 35.4, 20.4; IR (film) 3005, 2957, 2362, 2333, 1874, 1797, 1749, 1405, 1375, 1275, 1216, 1077, cm^{-1}.

*(S)-1-(4,4-Dibromobut-3-en-1-yl)-3-hydroxypyrrolidine-2,5-dione (**5a**).* An oven-dried 50 mL round-bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with (3*S*)-2,5-dioxotetrahydrofuran-3-yl acetate **4** (0.655 g, 4.14 mmol, 1.0 equiv) dissolved in dichloromethane (16 mL). The reaction mixture was cooled to 0 °C prior to the dropwise addition of 1,1-dibromo-4-amino-1-butene **3** (0.949 g, 4.14 mmol, 1.0 equiv). The solution was allowed to stir at 22 °C for 30 min and then was treated with triethylamine (61 μL, 0.43 mmol, 0.10 equiv). The reaction mixture was then stirred for 1 h at 22 °C and concentrated in vacuo to provide (*S*)-3-acetoxy-4-((4,4-dibromobut-3-en-1-yl)amino)-4-oxobutanoic acid as a crude yellow oil (1.60 g, 100%). The product was used without further purification.

An oven-dried 5 mL round-bottom flask equipped with a magnetic stirring bar, condenser, and nitrogen inlet was charged with 3-acetoxy-4-(4,4-dibromobut-3-enylamino)-4-oxobutanoic acid (0.462 g, 1.19 mmol, 1 equiv) and acetyl chloride (2.10 mL). The reaction mixture was allowed to stir at reflux for 4 h or until deemed complete by TLC. The reaction mixture was then concentrated, and the resulting dark brown

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oil was purified by flash chromatography (30% ethyl acetate in hexanes, R_f = 0.40) to provide (*S*)-1-(4,4-dibromobut-3-en-1-yl)-2,5-dioxopyrrolidin-3-yl acetate as a light yellow oil. Further purification was obtained by recrystallization from ethanol to provide a white solid (0.424 g, 96%).

An oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with (*S*)-1-(4,4-dibromobut-3-en-1-yl)-2,5-dioxopyrrolidin-3-yl acetate (0.260 g, 0.705 mmol, 1.0 equiv) suspended in ethanol (4 mL). The reaction mixture was cooled to 0 °C prior to the dropwise addition of acetyl chloride (0.150 mL, 2.15 mmol, 3.05 equiv), generating HCl in situ by reaction with the ethanol. The transparent-yellow reaction mixture was allowed to warm to 22 °C with stirring over 22 h or until deemed complete by TLC. The reaction mixture was then concentrated in vacuo to provide the title compound as a crude yellow oil. The crude product was purified by flash column chromatography (50% ethyl acetate in hexanes, R_f = 0.34) to provide the title compound as a white solid (0.228 g, 99%).

*(S)-1-(4,4-Dibromobut-3-en-1-yl)-3-hydroxypyrrolidine-2,5-dione (**5a**):* mp = 91−93 °C; $[\alpha]^{20}_D$ = −46.1 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-*d*) δ 6.38 (t, *J* = 7.5 Hz, 1H), 4.68 (ddd, *J* = 8.3, 4.8, 2.9 Hz, 1H), 3.77 (d, *J* = 3.1 Hz, 1H), 3.63 (t, *J* = 6.9 Hz, 2H), 3.10 (dd, *J* = 18.2, 8.3 Hz, 1H), 2.70 (dd, *J* = 18.2, 4.8 Hz, 1H), 2.41 (q, *J* = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 174.2, 134.3, 92.1, 67.1, 37.3, 36.6, 31.4; IR (film) 3431, 3028, 2947, 2850, 2359, 2340, 1783, 1701, 1634, 1558, 1541, 1507, 1442, 1439, 1402, 1350, 1317, 1261, 1171, 1104, 1058, 1024, 963, 903, 794, 755, 692, 614, 517, 509 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_8H_9Br_2NO_3$ 327.9002, found 327.9003.

*Intermediates from the Formation of **5a**. (S)-3-Acetoxy-4-((4,4-dibromobut-3-en-1-yl)amino)-4-oxobutanoic acid:* $[\alpha]^{20.8}_D$ = −1.3 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-*d*) δ 6.42 (m, 2H), 5.48 (t, *J* = 5.9 Hz, 1H), 3.40 (q, *J* = 6.2 Hz, 2H), 3.00 (dd, *J* = 5.9, 2.1 Hz, 2H), 2.37 (q, *J* = 7.0 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 170.2, 169.4, 135.2, 91.8, 69.9, 37.8, 36.4, 36.1, 33.2, 21.3, 20.9; IR (film) 3331, 3095, 2935, 2852, 2590, 2361, 2335, 1739, 1651, 1551, 1429, 1369, 1228, 1103, 1058, 944, 807, 784, 739, 628 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{13}Br_2NO_5$ 407.9053, found 407.9057.

(S)-1-(4,4-Dibromobut-3-en-1-yl)-2,5-dioxopyrrolidin-3-yl acetate: mp 57−59 °C; $[\alpha]^{22}_D$ = −10.3 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-*d*) δ 6.39 (t, *J* = 7.5 Hz, 1H), 5.43 (dd, *J* = 8.7, 4.7 Hz, 1H), 3.66 (t, *J* = 7.0 Hz, 2H), 3.18 (dd, *J* = 18.4, 8.7 Hz, 1H), 2.68 (dd, *J* = 18.4, 4.7 Hz, 1H), 2.43 (q, *J* = 7.0 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.38, 173.12, 169.95, 134.2, 92.1, 67.5, 36.7, 35.8, 31.3, 20.7; IR (film) 3487, 3028, 2948, 2947, 2850, 2360, 2337, 1790, 1749, 1716, 1714, 1712, 1635, 1558, 1541, 1507, 1439, 1437, 1403, 1371, 1353, 1316, 1250, 1226, 1165, 1106, 1040, 976, 872, 791, 692, 627, 591, 518 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{11}Br_2NO_4$ 391.8927 and [M + H]$^+$ 369.9108, found 391.8938 and 369.9124, respectively.

*(S)-3-((tert-Butyldimethylsilyl)oxy)-1-(4,4-dibromobut-3-en-1-yl)-pyrrolidine-2,5-dione (**5b**).* An oven-dried 50 mL round-bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with pyrrolidinedione **5a** (1.00 g, 3.06 mmol, 1.0 equiv), TBS-Cl (0.533 g, 3.67 mmol, 1.20 equiv), and imidazole (0.520 g, 7.65 mmol, 2.5 equiv) in dry DMF (2 mL) at room temperature. The yellowish reaction mixture was allowed to stir at 25 °C for 36 h or until deemed complete by TLC (1:1 ethyl acetate in hexanes, R_f = 0.91 (**5b**), 0.34 (**5a**)). The reaction mixture was then diluted and extracted with 1:1 ether−pentane (3 × 15 mL) and the organic layer washed with NH_4Cl (2 × 15 mL), brine (15 mL) and dried over anhydrous sodium sulfate. The solvents were then removed under reduced pressure to provide the crude product as a yellow oil. The crude product was purified by flash column chromatography (10% ethyl acetate in hexanes, R_f = 0.35) to furnish the title compound **5b** as a white solid (1.35 g, 100%): mp 27−29 °C; $[\alpha]^{19.7}_D$ = −29.3 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, chloroform-*d*) δ 6.37 (t, *J* = 7.4 Hz, 1H), 4.58 (dd, *J* = 8.2, 4.5 Hz, 1H), 3.61 (t, *J* = 6.9 Hz, 2H), 3.01 (dd, *J* = 18.0, 8.2 Hz, 1H), 2.60 (dd, *J* = 18.0, 4.5 Hz, 1H), 2.40 (q, *J* = 6.9 Hz, 2H), 0.92 (s, 9H), 0.18 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 174.1, 134.4, 91.8, 68.0, 39.0, 36.3, 31.5, 25.8, 18.4, −4.5, −5.1; IR (film) 3483, 3028, 2954, 2932, 2884, 2858, 2710, 2359, 2340, 1790, 1712, 1628, 1475, 1435, 1402, 1350, 1254, 1162, 1102, 1036, 944, 836, 781, 692, 670 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{23}Br_2NO_3Si$ 441.9867, found 441.9845.

Preparation for $TMSCH_2MgCl$. A flame-dried 250 mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, addition funnel, condenser and nitrogen inlet was charged with magnesium turnings (3.525 g, 144.5 mmol, 1.10 equiv) and THF (62 mL), followed by 1,2-dibromoethane (0.200 mL, 2.32 mmol). The magnesium suspension was stirred for 10 min, and chloromethyltrimethylsilane (18.33 mL, 131.3 mmol, 1.0 equiv) was added dropwise over 2 h during which time exotherms resulted in a gentle reflux of the reaction mixture. Following addition, the dark gray reaction mixture was stirred for 4 h at 22 °C and stirring then stopped. The reaction mixture was allowed to stand overnight. Concentrations were determined by titration using 2-butanol and 1,10-phenanthroline as an indicator.

Preparation for $Zn(CH_2TMS)_2$. A 250 mL flask was charged with $ZnCl_2$ and fused (melted) under high vacuum via a Bunsen burner. The resultant dry $ZnCl_2$ (6.58 g, 48.3 mmol) was dissolved in freshly distilled THF (48 mL) to form a 1 M stock solution. This solution was stored under N_2. A separate 25 mL round bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with 1 M $ZnCl_2$ (5 mL, 5 mmol, 1 equiv) solution. Over 15 min, at 0 °C, $TMSCH_2MgCl$ (5.10 mL, 10.0 mmol, 1.96 M, 2.0 equiv) was added. The reaction mixture became thick with a white precipitate, which required settling before use. The resulting light-gray supernatant was 1 M $Zn(CH_2TMS)_2$.

*(S)-3-((tert-Butyldimethylsilyl)oxy)-1-(5-(trimethylsilyl)-4-((trimethylsilyl)methyl)pent-3-en-1-yl)pyrrolidine-2,5-dione (**6**).* To an oven-dried 25 mL round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with *gem*-dibromide **5b** (0.967 g, 2.19 mmol, 1 equiv) dissolved in THF (6.58 mL) freshly distilled from sodium metal. The solution was then treated with $Zn(CH_2TMS)_2$ (4.38 mL, 4.38 mmol, 1 M in THF, 2.0 equiv) in portions and stirred for 5 min at 0 °C. Afterward, $PdCl_2(PPh_3)_2$ (0.107 g, 0.153 mmol, 7 mol %) was added all at once, and the flask was purged with N_2 and allowed to warm to room temperature.[26] The yellow suspension began to disappear once it reached 22 °C. The reaction was allowed to stir for 11 h 45 min at 22 °C. The light-orange reaction mixture was then poured over cold satd NH_4Cl (25 mL), extracted with ethyl ether (3 × 25 mL), and washed with brine (25 mL). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. Trituration of the residue with pentane (2 × 10 mL) followed by Celite (1/4 in.) filtration of the supernatant liquid afforded a crude product as a yellow oil, which was purified by flash column chromatography (SiO_2, gradient: hexanes then 5% → 10% ethyl acetate in hexanes) to provide the title compound as a colorless oil (0.228 g, 97%): $[\alpha]^{21}_D$ = −19.1 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-*d*) δ 4.72 (t, *J* = 7.1 Hz, 1H), 4.55 (dd, *J* = 8.2, 4.5 Hz, 1H), 3.47 (t, *J* = 7.5 Hz, 2H), 2.98 (dd, *J* = 17.9, 8.2 Hz, 1H), 2.58 (dd, *J* = 17.9, 4.5 Hz, 1H), 2.21 (q, *J* = 7.5 Hz, 2H), 1.47 (s, 2H), 1.40 (s, 2H), 0.92 (s, 9H), 0.18 (d, *J* = 3.6 Hz, 6H), 0.02 (s, 9H), −0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 174.3, 138.4, 114.3, 68.0, 38.96, 38.92, 29.7, 27.0, 25.8, 23.9, 18.4, −0.6, −1.0, −4.5, −5.1; IR (film) 3481, 2954, 2928, 2359, 1788, 1715, 1469, 1400, 1362, 1252, 1152, 1092, 837, 780, 624 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{45}NO_3Si_3$ 456.2780, found 456.2789.

Preparation of Lithiobutyne. To a flame-dried 100 mL Schlenk flask equipped with a magnetic stirring bar and nitrogen inlet was charged with THF (15 mL) and 1-butyne (3.25 g, 60.0 mmol, 1.2 equiv) at −10 °C (salt−ice bath). The solution was then cooled to −78 °C and treated dropwise with nBuLi (23.8 mL, 50.0 mmol, 1.0 equiv, 2.13 M in hexanes). After stirring for 30 min at −78 °C, the solution was allowed to slowly warm to 0 °C. The solvent was then removed to provide lithiobutyne as a white solid.

*(S)-4-((tert-Butyldimethylsilyl)oxy)-5-(but-1-yn-1-yl)-5-hydroxy-1-(5-(trimethylsilyl)-4-((trimethylsilyl)methyl)pent-3-en-1-yl)-pyrrolidin-2-one (**7**). Method 1.* An oven-dried 10 mL round-bottom

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flask equipped with a magnetic stirring bar and nitrogen inlet was charged with lithiobutyne (47.4 mg, 0.789 mmol, 1.20 equiv) dissolved in LPDE (5 M, 3.3 mL) at 0 °C. The cooled solution was then treated dropwise with a solution of imide **6** (0.300 g, 0.658 mmol, 1.0 equiv in 1.50 mL anhydrous ethyl ether) over a period of 2 min. Following complete addition, the reaction mixture was allowed to warm to room temperature and was stirred for 15 min or until deemed complete by TLC (15% ethyl acetate in hexanes). The reaction mixture was then diluted (2 mL Et_2O), poured over cold 5% NH_4OH (10 mL), extracted with Et_2O (3 × 10 mL), and dried over magnesium sulfate. Following the removal of solvents, the crude product was provided as a white solid (314 mg, 94%) that could be purified, and the diastereomers were separated by column chromatography (SiO_2, gradient: hexanes then 5% → 10% ethyl acetate in hexanes) to provide both as white solids (**7a**:**7b** = 26:74, 270 mg, 81%).

Method 2. An oven-dried 25 mL round-bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with lithiobutyne (0.153 g, 2.56 mmol, 3.00 equiv) in tetrahydrofuran (5.3 mL). The reaction mixture was cooled to −78 °C prior to the dropwise addition of cyclic imide **6** (0.389 g, 0.855 mmol, 1.0 equiv in 1.60 mL THF) over 20 min. The red-pink reaction mixture was then allowed to warm to −20 °C and was stirred at that temperature for 16 h. The reaction mixture was then quenched by slow addition of 1 M Et_3NHOAc in THF (5 mL) and extracted with water (10 mL), ether (3 × 10 mL), and the organic layer was washed with brine (10 mL). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to provide the desired product as a yellow oil. The crude product was purified by flash column chromatography (SiO_2, gradient: hexanes then 5% → 10% ethyl acetate in hexanes) to furnish the title compound as a light orange oil (**7a**:**7b** = 85:15, 0.368 g, 85%): HRMS (ESI-TOF) m/z $[M + H]^+$Calcd for $C_{26}H_{51}NO_3Si_3$ 510.3250; Found 510.3245.

7a: $[\alpha]^{18.9}_D$ = −15.5 (*c* 0.062, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-*d*) δ 4.79 (t, *J* = 7.2 Hz, 1H), 4.34 (t, *J* = 5.9 Hz, 1H), 3.96 (s, 1H), 3.39 (m, 1H), 3.24 (m, 1H), 2.63 (dd, *J* = 16.6, 6.9 Hz, 1H), 2.44−2.16 (m, 5H), 1.51 (s, 2H), 1.40 (s, 2H), 1.15 (t, *J* = 7.5 Hz, 3H), 0.93 (s, 9H), 0.16 (d, *J* = 7.1 Hz, 6H), 0.01 (d, *J* = 9.6 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 136.7, 115.6, 88.2, 84.6, 77.5, 77.0, 76.6, 73.4, 40.7, 38.3, 29.5, 28.4, 25.7, 23.8, 18.1, 13.4, 12.3, −0.7, −1.1, −4.7, −4.9; IR (film) 3479, 3334, 2951, 2932, 2894, 2856, 2240, 1712, 1404, 1362, 1316, 1248, 1146, 1081, 982, 952, 925, 837, 784, 700, 624 cm^{-1}.

7b: $[\alpha]^{18.4}_D$ = +14.1 (*c* 0.152, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-*d*) δ 4.83 (t, *J* = 7.0 Hz, 1H), 4.15 (d, *J* = 5.6 Hz, 1H), 3.55 (dt, *J* = 14.3, 7.7 Hz, 1H), 3.25 (dt, *J* = 14.3, 7.7 Hz, 1H), 2.96 (s, 1H), 2.76 (dd, *J* = 16.5, 5.6 Hz, 1H), 2.28 (m, 5H), 1.47 (dd, *J* = 22.4, 7.4 Hz, 4H), 1.18 (t, *J* = 7.5 Hz, 3H), 0.90 (s, 9H), 0.12 (d, *J* = 4.4 Hz, 6H), 0.02 (d, *J* = 5.0 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 138.4, 116.2, 91.5, 89.9, 77.6, 77.2, 76.8, 75.6, 74.9, 40.7, 39.2, 29.8, 28.7, 25.9, 24.3, 18.4, 13.6, 12.7, −0.4, −0.9, −4.5, −4.6; IR (film) 3140, 3057, 2954, 2927, 2894, 2852, 2246, 1655, 1453, 1389, 1362, 1317, 1245, 1139, 1078, 995, 930, 844, 783, 695, 628 cm^{-1}.

*(1S,7R,7aS)-7a-(But-1-yn-1-yl)-1-((tert-butyldimethylsilyl)oxy)-7-(3-(trimethylsilyl)prop-1-en-2-yl)hexahydro-3H-pyrrolizin-3-one (**8**).* *Method 1.* An oven-dried 50 mL round-bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with lithiobutyne (0.237 g, 3.94 mmol, 1.20 equiv) dissolved in LPDE (5 M, 16.45 mL) at 0 °C. The cooled solution was then treated dropwise with a solution of imide **6** (1.50 g, 3.29 mmol, 1.0 equiv in 7.50 mL anhydrous ethyl ether) over a period of 2 min. Following complete addition, the reaction mixture was allowed to warm to room temperature and was stirred for 15 min or until deemed complete by TLC (15% ethyl acetate in hexanes). The reaction mixture was then cooled to 0 °C and treated with TFAA[27] (0.56 mL, 3.9 mmol, 1.2 equiv). After being stirred for 12−15 min at room temperature (or until deemed complete by TLC; 15% EtOAc in hexanes) the reaction was quenched by inverse addition over cold 5% NH_4OH (20 mL) and extracted with ether (3 × 20 mL), and the organic layer was washed with brine (30 mL). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to furnish the title compound as an orange oil. The crude product was purified by flash column chromatography (SiO_2, gradient: hexanes then 5% → 10% → 15% ethyl acetate in hexanes) to furnish the title compound as a light yellow oil (695.3 mg, 50%).

Method 2. An oven-dried 5 mL round-bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with hydroxylactam **7** (0.033 g, 0.063 mmol, 1.0 equiv) in 5 M LPDE (0.314 mL, 0.20 M in substrate) at 0 °C. The reaction mixture was allowed to slowly warm to 22 °C and was stirred at that temperature for 15 h or until deemed complete by GC analysis. The reaction mixture was then diluted with cold 5% NH_4OH (5 mL) and extracted with ether (3 × 10 mL), and the organic layer washed with brine (15 mL). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to furnish a crude mixture of inseparable bicyclic lactams **8** and **9** as yellow oils (28% **8**; 8% **9**). The mixture may be partially purified by flash column chromatography (SiO_2, gradient: hexanes then 5% → 10% → 15% ethyl acetate in hexanes) or separated by reversed-phase HPLC to provide a yellow oil (7.62 mg, 28%).

Note: HPLC purifications resulted in diminished yields (∼10%)

Reversed-phase HPLC purification was performed with a Waters 2487 Dual λ Absorbance detector, 600 controller and pump, and a Phenomenex Synergi 4 μ Polar RP 80A HPLC column (250 × 21.2 mm) using Waters Empower 3 software. A gradient of A 0.1% TFA, H_2O) and B (0.1% TFA, 19:1 CH_3CN, H_2O) was used.

8: $[\alpha]^{21.2}_D$ = +29.9 (c 0.65, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-*d*) δ 4.69 (s, 1H), 4.55 (s, 1H), 4.12 (dd, *J* = 10.1, 7.2 Hz, 1H), 3.76 (ddd, *J* = 11.6, 7.5, 4.1 Hz, 1H), 3.04 (dt, *J* = 11.6, 7.5 Hz, 1H), 2.85 (t, *J* = 7.1 Hz, 1H), 2.71 (dd, *J* = 15.0, 10.1 Hz, 1H), 2.47 (dd, *J* = 15.0, 7.2 Hz, 1H), 2.24 (q, *J* = 7.4 Hz, 2H), 2.12 (dq, *J* = 11.6, 7.0 Hz, 1H), 1.83 (m, 2H), 1.61 (d, *J* = 13.3 Hz, 1H), 1.14 (t, *J* = 7.4 Hz, 3H), 0.90 (s, 9H), 0.03 (s, 15H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 171.6, 145.3, 108.6, 88.3, 79.2, 71.2, 70.9, 54.8, 42.9, 41.3, 31.2, 29.4, 25.8, 18.1, 14.2, 12.7, −1.2, −3.5, −4.8; IR (film) 3251, 3084, 2953, 2929, 2892, 2857, 2359, 2335, 2236, 1708, 1629, 1470, 1409, 1389, 1361, 1320, 1248, 1145, 918, 836, 777 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{41}NO_2Si_2$ 420.2749, found 420.2756.

9: ^{1}H NMR (300 MHz, chloroform-*d*) δ 4.92 (s, 1H), 4.86 (s, 1H), 4.42 (t, *J* = 6.9 Hz, 1H), 3.97 (dt, *J* = 14.0, 5.2 Hz, 1H), 3.05 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.72−2.55 (m, 2H), 2.47−2.29 (m, 3H), 2.20 (q, *J* = 7.4 Hz, 3H), 1.92−1.67 (m, 2H), 1.12 (t, *J* = 7.4 Hz, 3H), 0.91 (s, 9H), 0.12 (d, *J* = 7.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 144.8, 115.8, 88.8, 79.3, 75.0, 64.9, 43.2, 39.8, 39.3, 34.9, 25.9, 18.3, 14.1, 12.5, −4.6, −4.6; IR (film) 3381, 3072, 2954, 2932, 2852, 2358, 2339, 1700, 1445, 1404, 1252, 1142, 1005, 929, 890, 833, 780, 666 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{33}NO_2Si$ 348.2353, found 348.2338.

Preparation of Lithium Diisobutylisopropoxyaluminum Hydride (LDBIPA). The desired reducing agent lithium diisobutylisopropoxyaluminum hydride (LDBIPA) was obtained as a colorless solution from DIBAL (1 M in toluene) by the general preparation procedure outlined by An.[19] Concentrations were determined by reaction with excess *p*-methoxybenzaldehyde and analysis of an aliquot by No-D ^{1}H NMR.[28]

*(1S,7R,7aS)-7a-(But-1-yn-1-yl)-1-((tert-butyldimethylsilyl)oxy)-7-(3-(trimethylsilyl)prop-1-en-2-yl)hexahydro-1H-pyrrolizine-3-carbonitrile (**10**).* An oven-dried 5 mL round-bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with lactam **8** (0.405 g, 0.965 mmol, 1.0 equiv) dissolved in THF (1.98 mL). The solution was then cooled to 0 °C and treated dropwise with LDBIPA (2.49 mL, 1.45 mmol, 0.580 M, 1.50 equiv) over several minutes. The reaction mixture was allowed to slowly warm to 22 °C and stir for 24 h or until deemed complete by TLC (15% EtOAc in hexanes). Upon completion of the partial reduction, the reaction mixture was treated dropwise with freshly distilled TMSCN (0.340 mL, 2.70 mmol, 2.80 equiv) and allowed to stir at 22 °C for 7 h or until deemed complete by TLC. The reaction mixture was then quenched by slow addition of water (5 mL), filtered over Celite, and extracted from ethyl ether (3 × 10 mL). The combined extracts were dried over anhydrous

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sodium sulfate and concentrated in vacuo to provide desired product as an orange oil. The crude product was purified by flash column chromatography (SiO_2, gradient, hexanes then 5% → 10% ethyl acetate in hexanes) to furnish the title compound **10** as a diastereomeric mixture of light-yellow oils (75:25, 0.339 g, 82%): HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{42}N_2OSi_2$ 430.2836, found 430.2827

Major diastereomer: $[\alpha]^{19}_D$ = −7.0 (*c* 0.29, $CHCl_3$); ^1H NMR (300 MHz, chloroform-*d*) δ 4.78 (s, 1H), 4.69 (s, 1H), 4.46 (d, *J* = 5.8 Hz, 1H), 4.05 (dd, *J* = 9.3, 5.5 Hz, 1H), 3.23−3.12 (app m, 2H), 2.91 (dd, *J* = 12.8, 6.0 Hz, 1H), 2.39−2.19 (m, 4H), 2.15 (d, *J* = 13.4 Hz, 1H), 2.09−1.91 (m, 1H), 1.80−1.70 (m, 1H), 1.61 (d, *J* = 13.4 Hz, 1H), 1.13 (t, *J* = 7.5 Hz, 3H), 0.90 (s, 9H), 0.07 (d, *J* = 1.0 Hz, 6H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 118.5, 108.6, 88.9, 80.9, 77.6, 77.2, 76.8, 73.0, 72.6, 55.4, 50.7, 50.1, 39.1, 29.0, 28.6, 25.9, 18.1, 13.9, 12.8, −1.2, −3.6, −4.7; IR (film) 3084, 2958, 2932, 2894, 2860, 2361, 2342, 2240, 2224, 1792, 1704, 1628, 1472, 1418, 1365, 1320, 1248, 1149, 1088, 1058, 1035, 1005, 944, 917, 860, 837, 776, 704, 635 cm^{-1}.

Minor diastereomer: $[\alpha]^{21.4}_D$ = +10.9 (*c* 0.162, $CHCl_3$); ^1H NMR (300 MHz, chloroform-*d*) δ 4.63 (d, *J* = 5.8 Hz, 2H), 3.81 (t, *J* = 7.4 Hz, 1H), 3.51 (t, *J* = 8.2 Hz, 1H), 3.22 (dt, *J* = 12.4, 9.3 Hz, 1H), 2.94−2.73 (m, 2H), 2.32−2.13 (m, 5H), 1.67 (dp, *J* = 10.1, 4.9 Hz, 2H), 1.55 (d, *J* = 13.3 Hz, 1H), 1.11 (t, *J* = 7.5 Hz, 3H), 0.88 (s, 9H), 0.14 − −0.15 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 119.1, 108.1, 88.9, 80.7, 72.7, 55.9, 52.9, 38.7, 28.4, 27.6, 25.8, 18.1, 13.9, 12.9, −1.2, −3.6, −4.7; IR (film) 3084, 2954, 2928, 2890, 2860, 2361, 2339, 2240, 1784, 1700, 1628, 1476, 1418, 1358, 1324, 1244, 1152, 1103, 1084, 1009, 948, 902, 856, 837, 780, 704, 666, 643 cm^{-1}.

*(1R,5S,7S,7aS)-7a-(But-1-yn-1-yl)-7-((tert-butyldimethylsilyl)oxy)-9-methylenehexahydro-1H-1,5-ethanopyrrolizine (**11**).* An oven-dried 5 mL round-bottom flask equipped with a magnetic stirring bar and nitrogen inlet was charged with $AgBF_4$ (in a drybox, 30.12 mg, 0.1547 mmol, 1.10 equiv) followed by cyanoamine **10** (60.6 mg, 0.141 mmol, 1 equiv) dissolved in THF (1.81 mL). The reaction mixture was then protected from light and allowed to stir at 22 °C for 22 h or until deemed complete by GC/TLC. The reaction mixture was then quenched by the addition of 5% NH_4OH (2.5 mL) and extracted from ethyl ether (4 × 5 mL). The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to provide the desired product **11** as a brown oil. The brown oil may then be purified by trituration with pentane (5 mL) followed by passing over a plug of alumina (neutral, activity II, elute with 100% EtOAc) to provide the title compound as a dark orange oil (41.1 mg, 88%): $[\alpha]^{20.7}_D$ = +110.2 (*c* 0.33, $CHCl_3$); ^1H NMR (300 MHz, chloroform-*d*) δ 4.65 (s, 1H), 4.59 (s, 1H), 4.26 (dd, *J* = 7.6, 4.8 Hz, 1H), 3.47−3.18 (m, 2H), 3.01 (ddd, *J* = 13.3, 8.6, 5.4 Hz, 1H), 2.69 (d, *J* = 6.2 Hz, 1H), 2.38−2.11 (m, 4H), 2.04 (dddd, *J* = 13.0, 6.7, 4.8, 2.1 Hz, 1H), 1.91 (dd, *J* = 13.0, 7.6 Hz, 1H), 1.69−1.53 (m, 2H), 1.11 (t, *J* = 7.5 Hz, 3H), 0.90 (s, 9H), 0.08 (d, *J* = 4.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 107.7, 87.5, 78.4, 75.3, 72.7, 62.0, 55.0, 46.9, 43.4, 34.2, 31.7, 26.1, 18.5, 14.2, 12.9, −4.5, −4.7; IR (film) 3396, 2951, 2932, 2856, 2361, 2342, 1712, 1651, 1469, 1362, 1316, 1252, 1122, 1103, 1005, 936, 841, 776, 666 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{33}NOSi$ 332.2404, found 332.2407.

*(1R,5S,7S,7aS)-7a-(But-1-yn-1-yl)-9-methylenehexahydro-1H-1,5-ethanopyrrolizin-7-ol (**12**).* A PTFE plastic flask equipped with a magnetic stirring bar was charged with tricycle **11** (0.1173 g, 0.3537 mmol, 1.0 equiv) dissolved in acetonitrile (11.8 mL). The solution was then treated with aqueous HF (48%, 0.62 mL) and allowed to stir for 24 h at 22 °C or until deemed complete by TLC (5% MeOH in DCM + 1% NH_4OH). The reaction mixture was then quenched by the addition of 1 M KOH (18 mL) and extracted from ethyl ether (3 × 20 mL). The combined extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to provide the desired product as a yellow solid. The crude product was purified by bulb-to-bulb distillation (1 mmHg, 140−160 °C) to furnish the title compound **12** as a white solid (73.2 mg, 95%): mp 174−176 °C (sublime); $[\alpha]^{20.3}_D$ = +237.7 (*c* 0.039, $CHCl_3$); ^1H NMR (300 MHz, chloroform-*d*) δ 4.67 (s, 1H), 4.63 (s, 1H), 4.21 (app t, *J* = 6.1 Hz, 1H), 3.41 (d, *J* = 4.0 Hz, 1H), 3.26 (ddd, *J* = 13.1, 10.6, 4.2 Hz, 1H), 3.07 (ddd, *J* = 13.1, 8.6, 5.5 Hz, 1H), 2.77 (d, *J* = 6.1 Hz, 1H), 2.44 (s, 1H), 2.35 (s, 1H), 2.33−2.20 (m, 3H), 2.03 (ddd, *J* = 6.1, 4.0, 1.3 Hz, 2H), 1.73−1.61 (m, 2H), 1.15 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 108.5, 90.4, 76.9, 75.95, 71.1, 62.3, 54.4, 46.8, 41.8, 34.2, 31.8, 14.2, 12.7; IR (film) 3161, 3076, 2965, 2925, 2850, 2359, 2340, 2245, 1646, 1442, 1376, 1317, 1251, 1098, 981, 906, 884, 814, 722, 670 cm^{-1} ; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{19}NO$ 218.1539, found 218.1547.

*(1R,5S,7aS)-7a-(But-1-yn-1-yl)-9-methylenehexahydro-7H-1,5-ethanopyrrolizin-7-one (**13**).* A 10 mL round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with tricycle **12** (73.20 mg, 0.3368 mmol, 1.0 equiv) in dichloromethane (2.9 mL). To the stirred solution was added Dess−Martin periodinane (15 wt % in CH_2Cl_2, 1.20 mL, 0.573 mmol, 1.70 equiv) dropwise at room temperature. The reaction progress was monitored TLC analysis (silica gel, 9:1 CH_2Cl_2−MeOH). The reaction mixture was then quenched with the addition of sodium hydroxide (1 M, 4 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine (5 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to provide the desired product as a yellow oil. Washing of the viscous oil with pentane (3 × 2 mL) followed by concentration of the triturate furnished the title compound (68.5 mg, 95%) as a light-yellow viscous oil. The product was used without further purification: $[\alpha]^{20}_D$ = +227.1 (*c* 0.29, $CHCl_3$); ^1H NMR (300 MHz, chloroform-*d*) δ 4.71 (s, 1H), 4.65 (s, 1H), 3.60 (dd, *J* = 6.9, 4.5 Hz, 1H), 3.39 (ddd, *J* = 13.4, 10.8, 4.1 Hz, 1H), 3.20 (ddd, *J* = 13.4, 8.3, 5.6 Hz, 1H), 3.01 (d, *J* = 6.0 Hz, 1H), 2.68 (ddd, *J* = 17.5, 6.9, 1.7 Hz, 1H), 2.55 (ddd, *J* = 14.4, 4.5, 2.2 Hz, 1H), 2.37−2.04 (m, 4H), 1.92−1.75 (m, 2H), 1.10 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 143.8, 110.8, 88.4, 74.8, 57.0, 56.1, 49.0, 43.8, 33.5, 31.6, 13.9, 12.7; IR (film) 3072, 2974, 2939, 2878, 2848, 2361, 2339, 2244, 1761, 1647, 1469, 1442, 1396, 1332, 1275, 1221, 1183, 1168, 1149, 1126, 1092, 1073, 1016, 997, 932, 909, 860, 799, 765, 723, 598, 545 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{17}NO$ 216.1383, found 216.1386.

*(1R,5S,7R,7aS)-7a-(But-1-yn-1-yl)-9-methylenehexahydro-1H-1,5-ethanopyrrolizin-7-ol (**14**).* A 10 mL round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with tricycle **13** (68.5 mg, 0.318 mmol, 1.0 equiv) dissolved in THF (3.2 mL). Then the mixture was cooled to 0 °C prior to the dropwise addition of LDBIPA (0.582 M, 0.820 mL, 0.477 mmol, 1.50 equiv), and the reaction progress was monitored by TLC (9:1 CH_2Cl_2−MeOH). Upon completion (24 h), the reaction was then quenched by slow addition of water (4 mL) and extracted with ethyl ether (3 × 5 mL). The combined extracts were filtered over a Celite plug, dried over anhydrous magnesium sulfate, and concentrated in vacuo to provide desired product as a yellow oil (67.5 mg, 98%). The crude product may then be recrystallized by dissolving in pentane and cooling to −30 °C to induce crystallization to provide the desired azatricycle as a white solid (63.5 mg, 92%): mp 74−75 °C; $[\alpha]^{21.7}_D$ = +136.2 (*c* 0.149, $CHCl_3$); ^1H NMR (300 MHz, chloroform-*d*) δ 4.91 (s, 1H), 4.77 (s, 1H), 4.58 (ddd, *J* = 12.8, 10.7, 2.8 Hz, 1H), 3.36 (dd, *J* = 6.9, 4.6 Hz, 1H), 3.26 (ddd, *J* = 13.1, 10.5, 4.1 Hz, 1H), 3.03 (ddd, *J* = 13.1, 8.5, 5.5 Hz, 1H), 2.95 (d, *J* = 6.1 Hz, 1H), 2.85 (d, *J* = 12.8 Hz, 1H), 2.69 (dddd, *J* = 14.0, 10.7, 6.9, 1.8 Hz, 1H), 2.50 (ddd, *J* = 14.9, 4.6, 2.3 Hz, 1H), 2.40−2.25 (m, 1H), 2.19 (q, *J* = 7 .5 Hz, 2H), 1.85 (d, *J* = 14.9 Hz, 1H), 1.62 (ddd, *J* = 12.7, 8.5, 4.1 Hz, 1H), 1.28 (dd, *J* = 14.0, 2.8 Hz, 1H), 1.11 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 108.9, 85.6, 80.1, 78.2, 72.9, 60.8, 52.1, 47.6, 40.3, 34.8, 32.9, 14.1, 12.7; IR (film) 3538, 3316, 3072, 2961, 2925, 2854, 2736, 2529, 2470, 2359, 2340, 2241, 1761, 1735, 1650, 1450, 1317, 1257, 1162, 1106, 1077, 1017, 888, 799, 729, 570 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{20}NO$ 218.1539, found 218.1529.

*(1R,5S,7R,7aS)-7a-(But-1-yn-1-yl)-9-methylenehexahydro-1H-1,5-ethanopyrrolizin-7-ol Ammonium Trifluoroacetate (**14·TFA**).* A 5 mL round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with tricycle **14** (67.5 mg, 0.311 mmol, 1.0 equiv) dissolved in Et_2O (6 mL). The solution was treated with

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TFA (26.3 μL, 0.342 mmol, 1.10 equiv) dropwise with stirring at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was concentrated in vacuo, and the resulting viscous oil was washed with pentane (3 × 5 mL). The residue was dissolved in Et_2O and filtered through a Celite plug to furnish the crude compound as a light yellow oil. The crude oil was then purified by column chromatography (SiO_2, gradient, 100% EtOAc → 7:1 EtOAc−MeOH; R_f = 0.37) to provide trifluoroacetate salt **14·TFA** as a nearly colorless oil (95.5 mg, 93%): $[\alpha]^{21}_D$ = +58.4 (*c* 0.24, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-*d*) δ 5.08 (s, 1H), 4.96 (s, 1H), 4.77 (dd, *J* = 10.7, 2.9 Hz, 1H) 3.86 (s, 1H), 3.71−3.57 (app m, 1H), 3.34 (ddd, *J* = 13.7, 8.7, 6.0 Hz, 1H), 3.16 (d, *J* = 6.1 Hz, 1H), 3.04−2.88 (m, 1H), 2.70 (d, *J* = 15.9 Hz, 1H), 2.64−2.50 (m, 1H), 2.30−2.09 (m, 3H), 1.79 (ddd, *J* = 12.9, 8.7, 4.1 Hz, 1H), 1.53 (dd, *J* = 14.3, 2.9 Hz, 1H), 1.13 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 113.2, 90.6, 75.9, 75.2, 73.6, 60.9, 52.1, 46.5, 38.6, 33.5, 30.8, 13.6, 12.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.46; IR (film) 3356, 2986, 2958, 2927, 2854, 2770, 2575, 2502, 2359, 2341, 2247, 1770, 1642, 1432, 1195, 1135, 1073, 1038, 961, 905, 833, 797, 721 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}NO$ 218.1539, found 218.1529.

*(1S,2a^{1}S,4R,5S,7aS)-2a^1-(But-1-yn-1-yl)hexahydro-1,4-methanofuro[2,3,4-gh]pyrrolizin-1(2aH)-ol Ammonium Trifluoroacetate (**15·TFA**).* A 10 mL double-necked round-bottomed flask equipped with a magnetic stirring bar and oxygen inlet was charged with tropane trifluoroacetate salt **14·TFA** (28.8 mg, 0.0869 mmol, 1.0 equiv) in dichloromethane (2.2 mL) at −78 °C (dry ice−acetone bath). Ozone was bubbled into the solution at an oxygen pressure of 8 psi, 110 V, and a flow rate of 0.040 cu ft/min for 2 min or until a light-blue color persisted. The reaction mixture was then purged of excess ozone for 5 min using a stream of N_2 and treated with PPh_3 (25.0 mg, 0.0956 mmol, 1.10 equiv in 0.50 mL CH_2Cl_2). After being stirred for an additional 2 min, the reaction mixture was allowed to slowly warm to 22 °C, and solvent was removed to provide the crude mixture as a light yellow oil. The crude product was purified by reversed-phase HPLC (gradient, 25% CH_3CN to 5% CH_3CN in H_2O) to furnish the title compound **15·TFA** as a faint-yellow oil (24.3 mg, 84%).

Reversed-phase HPLC purification was performed with a Waters 2487 Dual λ Absorbance detector, 600 controller and pump, and a Phenomenex Synergi 4 μ Polar RP 80A HPLC column (250 × 21.2 mm) using Waters Empower 3 software. A gradient of A 0.1% TFA, H_2O) and B (0.1% TFA, 19:1 CH_3CN, H_2O) was used: $[\alpha]^{19}_D$ = +19.8 (*c* 0.238, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-*d*) δ 4.74 (s, 1H), 4.13 (s, 1H), 3.84 (td, *J* = 12.5, 5.4 Hz, 1H), 3.49 (m, 1H), 2.82 (d, *J* = 5.6 Hz, 1H), 2.56−2.34 (m, 2H), 2.27 (q, *J* = 7.5 Hz, 2H), 2.23−1.94 (m, 4H), 1.15 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 162.1, 161.6, 118.7, 114.8, 103.8, 95.4, 81.0, 78.5, 69.9, 61.9, 59.2, 47.5, 36.9, 32.2, 23.8, 13.2, 12.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.32; IR (film) 3224, 2981, 2943, 2925, 2882, 2852, 2761, 2602, 2551, 2361, 2339, 2251, 1670, 1480, 1457, 1430, 1358, 1282, 1199, 1134, 1077, 1062, 978, 898, 833, 799, 719, 662, 571, 537 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}NO_2$ 220.1332, found 220.1333.

*(1S,2a^{1}R,4R,5S,7aS)-2a^1-Butylhexahydro-1,4-methanofuro[2,3,4-gh]pyrrolizin-1(2aH)-ol Ammonium Trifluoroacetate (**16a**).* A 10 mL round-bottomed flask equipped with a magnetic stirring bar and hydrogen inlet was charged with Pd/C (5 wt %, 27.6 mg, 0.0130 mmol, 0.20 equiv) and hemiketal trifluoroacetate salt **15·TFA** (21.7 mg, 0.0651 mmol, 1.0 equiv) in ethyl acetate (5.6 mL) at 22 °C. Reaction progress was monitored by TLC (7:1 EtOAc in MeOH). Following reaction completion (approximately 3 h), the reaction mixture was filtered over Celite and concentrated in vacuo to afford the title compound as a crude oil. The product was then purified by column chromatography (SiO_2, gradient, 100% EtOAc to 7:1 EtOAc in MeOH) to furnish the pure stemofoline core as the trifluoroacetate salt **16a** as a colorless oil (17.1 mg, 78%): $[\alpha]^{19.1}_D$ = +28.1 (*c* 0.079, $CHCl_3$); ^{1}H NMR (300 MHz, chloroform-*d*) δ 4.55 (s, 1H), 4.10 (s, 1H), 3.71 (ddd, *J* = 13.6, 11.1, 5.8 Hz, 1H), 3.44 (m, 1H), 2.65 (d, *J* = 6.1 Hz, 1H), 2.33−2.05 (m, 5H), 2.03−1.89 (m, 2H), 1.76 (dt, *J* = 16.4, 6.6 Hz, 1H), 1.40 (dp, *J* = 16.4, 5.7 Hz, 4H), 0.97−0.87 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.0, 86.9, 78.1, 77.6, 62.1, 54.5, 46.9, 36.4, 32.8, 28.8, 26.9, 23.4, 22.9, 14.0; ^{19}F NMR (282 MHz, C_6D6) δ −75.45; IR (film) 3271, 2961, 2935, 2871, 2768, 2614, 2546, 2360, 2342, 1673, 1466, 1427, 1360, 1197, 1133, 1088, 1023, 982, 838, 796, 721 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{21}NO_2$ 224.1645, found 224.1652.

*(1S,2a^{1}R,4R,5S,7aS)-2a^1-((E)-But-1-en-1-yl)hexahydro-1,4-methanofuro[2,3,4-gh]pyrrolizin-1(2aH)-ol (**16b**).* A 10 mL double-necked round bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was charged with hemiketal trifluoroacetate salt **15·TFA** (12.9 mg, 0.0387 mmol, 1.0 equiv) dissolved in THF (2 mL) at room temperature. To the stirred solution was added *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (10.2 μL, 0.0387 mmol, 1.0 equiv) all at once, and the resulting solution was allowed to stir until completion (3 h). Upon completion, solvent and volatile byproducts were removed under high vacuum to provide the sensitive intermediate TMS protected hemiketal as a colorless oil which must be used immediately.

The TMS-protected hemiketal (15.6 mg, 0.0387 mmol, 1.0 equiv) was then dissolved in THF (1 mL) at room temperature. The stirred solution was cooled to −78 °C, equipped with a dry ice condenser, and charged with anhydrous liquid ammonia (3 mL). The cooled solution was then treated piecewise with sodium metal (8.70 mg, 0.395 mmol, 10.2 equiv) to provide a dark blue reaction mixture. The reaction mixture turned clear after 35 min and was then quenched by cautious addition of saturated NH_4Cl (1 mL), and the ammonia was evaporated by removal of the condenser and extracted using Et_2O (4 × 3 mL). The combined extracts were dried over anhydrous magnesium sulfate, concentrated in vacuo, and purified by extraction (3 × 5 mL MeOH/hexanes, product in MeOH) to provide the desired product as a colorless oil (4.71 mg, 55%): $[\alpha]^{20.6}_D$ = +2.3 (*c* 0.131, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 5.83 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.56−5.42 (m, 1H), 4.26 (s, 1H), 3.09 (s, 1H), 2.94 (ddd, *J* = 13.1, 9.7, 6.0 Hz, 1H), 2.61 (ddd, *J* = 13.1, 8.0, 5.2 Hz, 1H), 2.32 (d, *J* = 5.6 Hz, 1H), 1.95 (dq, *J* = 7.3, 6.5 Hz, 2H), 1.83−1.44 (m, 6H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 132.5, 129.0, 105.9, 83.3, 82.9, 61.5, 58.0, 48.8, 38.3, 35.4, 27.3, 26.0, 14.2; IR (film) 3338, 3027, 2962, 2874, 2749, 2602, 2361, 1742, 1670, 1559, 1472, 1453, 1347, 1328, 1297, 1285, 1259, 1225, 1195, 1134, 1095, 1058, 1023, 978, 944, 902, 876, 807, 722, 735, 700, 659, 586, 567, 541 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{20}NO_2$ 222.1489, found 222.1483.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01625.

^{1}H NMR, ^{13}C NMR, HSQC, and COSY spectra (PDF)

X-ray crystallographic data for compound **14** (PDF)

X-ray crystallographic data for compound **14** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*Tel: 406-994-5408. E-mail: livinghouse@chemistry.montana.edu.

Notes

The authors declare no competing financial interest.

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