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Application of an intramolecular dipolar cycloaddition to an asymmetric synthesis of the fully oxygenated tricyclic core of the stemofoline alkaloids

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Abstract

An intramolecular non-stabilized azomethine ylide dipolar cycloaddition was applied toward the first non-racemic synthesis of the fully oxygenated bridged pyrrolizidine core (**45**) of (+)-stemofoline (**1**) in 11 steps from a commercially available starting material.

1. Introduction

Stemofoline (**1**, Fig. 1) was first isolated from the stems and leaves of *Stemona japonica* by Irie and co-workers in 1970.[1] X-ray crystallographic analysis of the hydrobromide salt of **1** revealed a pyrrolizidine ring system containing a two-carbon bridge connecting C7 and C9a and an angular butyl side chain at C3. Stemofoline also contains a spiroketal functionality at C8 and a (*Z*)-olefin bridge from a tetrahydrofuran ring to a conjugated butenolide moiety. The rigid pentacyclic core of **1** possesses three heteroatoms and seven contiguous stereogenic centers.[2,3]

Of the 11 members of the stemofoline alkaloids which have been reported to date,[4–8] most differ only in the oxidation state of the C3 chain (cf. **1** vs **2** or **3**) or the (*E*)-configuration versus (*Z*)-configuration of the C11–C12 alkene (**1** vs **4**). Notably, Sekine and co-workers reported isolation of **2**, which they named asparagamine A, from the roots of *Asparagus racemosus*.[4] Later studies suggested that Sekine and co-workers had actually isolated **2** from *Stemona collinsae*, which

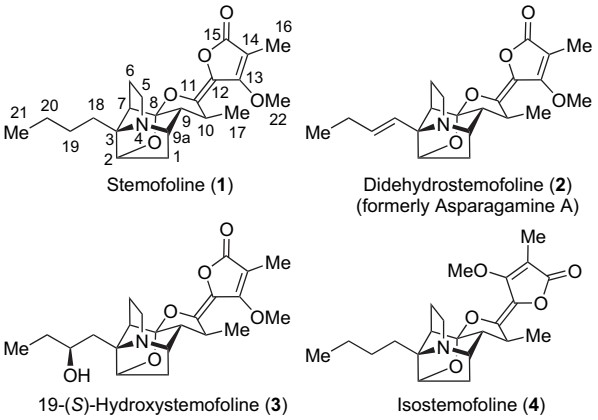

Figure 1. Selected stemofoline alkaloids.

is commonly confused with *A. racemosus*.[5] Parallel studies found **2** to be a major component of the ethanolic extracts of *S. collinsae*,[6] along with 19-(*S*)-hydroxystemofoline (**3**).[5] Since it appears to have no connection to the *Asparagus* plant genus, **2** is now commonly referred to as didehydrostemofoline.

The Thai plant from which Sekine and co-workers isolated didehydrostemofoline (**2**) had traditionally been administered to pregnant women to arrest premature uterine contractions, and it was hypothesized that **2** was the active agent. Indeed,

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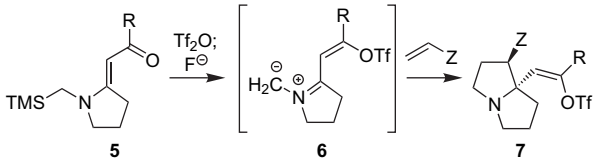
2 was found not only to inhibit oxytocin-induced labor in pregnant rats but also to exhibit dose-dependent in vivo activity against Kato-III human gastric carcinoma cells.[9] More recent explorations have focused on the potential of *Stemona* alkaloids as natural insecticides, as **1**–**3** were found to exhibit insecticidal and growth-inhibitory activity against the neonate larvae of *Spodoptera littoralis*.[5,10] Additionally, **1** and **2** have shown insecticidal and antifeedant activity against the larvae of the diamondback moth, a vegetable crop pest.[6]

Owing to their complex molecular architecture and intriguing biological activity, the stemofoline alkaloids have attracted considerable synthetic attention,[11–14] culminating in two racemic total syntheses.[15,16] The studies reported herein comprise the first non-racemic synthesis of the fully oxygenated tricyclic core of the stemofoline alkaloids.

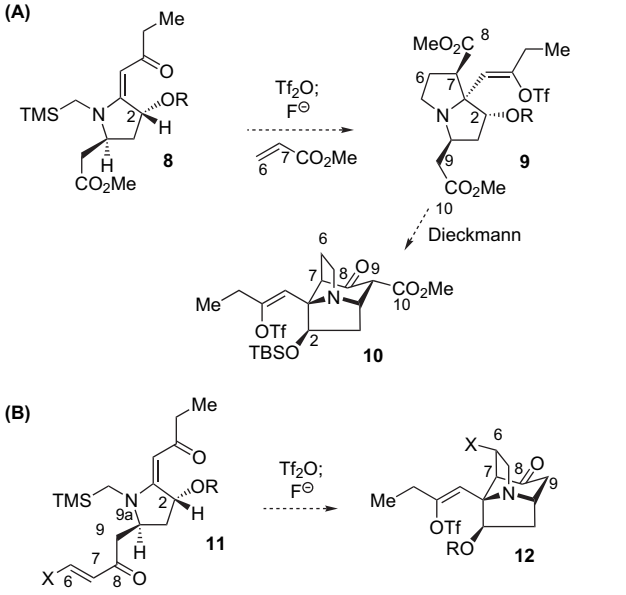
2. Results and discussion

The utility of azomethine ylide [3+2] cycloadditions for the construction of highly substituted pyrrolidine rings has been demonstrated by its implementation in the total synthesis of numerous alkaloid natural products.[17–21] Non-stabilized azomethine ylides are often generated by desilylation of iminium salts derived from the O-activation of amides[17,22] or the N-alkylation of vinylogous imidates.[23] In a related strategy, we recently reported the use of *N*-(trimethylsilyl)methyl vinylogous amides as precursors to azomethine ylides suitable for the preparation of substituted pyrrolizidines and indolizidines.[13] This method proceeded by O-activation of (trimethylsilyl)-methyl vinylogous amides such as **5** with trifluoromethanesulfonic (triflic) anhydride, followed by desilylation with the anhydrous fluoride source tetrabutylammonium triphenyldifluorosilicate (TBAT) to generate azomethine ylides such as **6**, which underwent [3+2] cycloadditions with a variety of electron-poor olefins (Scheme 1). Extension of the method to an intramolecular mode led to a synthesis of the C2-deoxy bridged pyrrolizidine core of the stemofoline alkaloids. Herein, we disclose the synthesis of the fully oxygenated core of this family of alkaloids, overcoming notable stereochemical impedances in installing the C2 oxygen functionality.



Scheme 1. Dipolar cycloadditions of azomethine ylides derived from vinylogous amides.

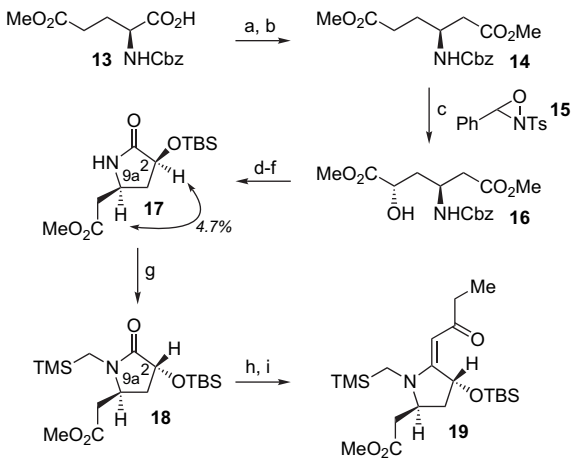
Two synthetic routes were explored (Scheme 2), one involving an intermolecular mode of the azomethine ylide cycloaddition and the other focusing on an intramolecular variant. In the former (Scheme 2A), vinylogous amide **8**, incorporating the requisite C2–OR group, was envisioned to be a suitable precursor to azomethine ylide formation, followed by *endo*-selective [3+2] cycloaddition with methyl acrylate to provide pyrrolizidine **9**. Subsequent transannular Dieckmann condensation



Scheme 2. Proposed synthesis of C2 oxygenated bridged pyrrolizidine core of the stemofoline alkaloids via inter- or intramolecular dipolar azomethine ylide cycloaddition.

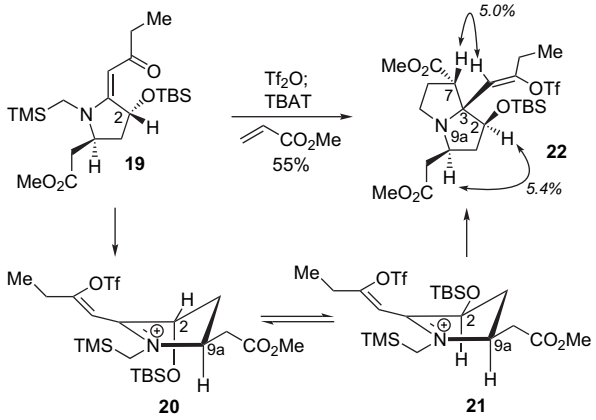
could then effect formation of the C8–C9 bond to provide bridged pyrrolizidine **10**, which directly maps onto the azapolycyclic substructure within stemofoline (**1**). Alternatively, in an intramolecular cycloaddition approach to the target (Scheme 2B), the more elaborate vinylogous amide **11**, incorporating both the C2–OR group and the C6–C7 dipolarophile, could be used to generate the azomethine ylide to trap the pendant electron-poor olefin, providing the suitably functionalized bridged pyrrolizidine **12** directly.

The intermolecular cycloaddition–Dieckmann approach began with Arndt–Eistert homologation of the readily available *N*-benzyloxycarbonyl-L-glutamic acid-5-methyl ester (**13**),[24] which provided bis(methyl ester) **14** (79%, Scheme 3). Selective α-hydroxylation of the ester distal to the N-functionality with Davis oxaziridine **15** allowed for introduction of the C2-oxygen group, providing the secondary alcohol **16** as a single diastereomer (52%). Hydrogenolysis of the benzyl carbamate to the corresponding primary amine was followed by lactamization in hot pyridine. Verification of stereochemistry was not conducted until silylation of the secondary alcohol in **16** to provide the lactam **17** (95%, three steps), whose *cis*-stereochemical relationship was established by an NOE signal between the C9a and C2 methine proton resonances. However, alkylation of **17** with (chloromethyl)trimethylsilane proceeded with epimerization of the C2 stereocenter to yield its C2-*R* configuration (60%).[25] Nevertheless, this was anticipated to be a welcome occurrence given that this C2 substituent can be envisioned to serve as a favorable stereochemical determinant in the key cycloaddition. Lactam **18** was converted to the corresponding (*E*)-vinylogous amide **19** via a two-pot sequence involving thionation with Lawesson's reagent (95%) followed by condensation of the resulting thiolactam with 1-bromo-2-butanone and phosphine-mediated Eschenmoser sulfide contraction (71%).



Scheme 3. (a) EtOCOCl, Et_3N, THF, 0 °C; CH_2N_2, Et_2O, −10 to 23 °C, 87%; (b) AgOAc, MeOH, 23 °C, 91%; (c) LHMDS, THF, −78 °C, 52%; (d) H_2 (1 atm), 10% Pd/C, MeOH, 23 °C; (e) pyridine, 100 °C; (f) TBSCl, imidazole, pyridine, 23 °C, 95% (three steps); (g) NaH, $TMSCH_2Cl$, DMF, 23 °C, 60%; (h) Lawesson's reagent, PhMe, 65 °C, 95%; (i) 1-bromo-2-butanone, 60 °C; Ph_3P, Et_3N, CH_2Cl_2, 23 °C, 71%.

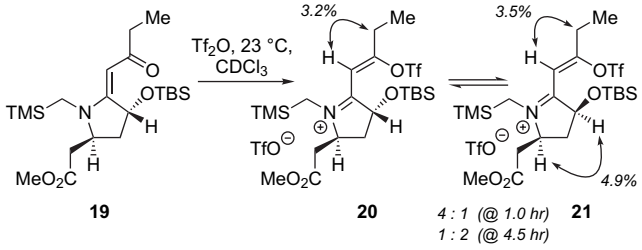
In accordance with the cycloaddition method previously developed in our laboratories, vinylogous amide **19** was treated sequentially with Tf_2O and TBAT in the presence of the dipolarophile methyl acrylate (Scheme 4). It was anticipated that the α-oriented C2−OTBS ether would bias approach of the dipolarophile onto the β-face of the transient azomethine ylide in an *endo*-transition state to provide the cycloadduct **9**, originally depicted in Scheme 2A. Although a regio- and *endo*-selective cycloaddition ensued, it proceeded with an unexpected stereochemical outcome with the isolation of the pyrrolizidine **22** (55%, Scheme 4). The structure of **22**, a result consistent with in situ C2-epimerization leading to α-approach of the dipolarophile, was verified by a battery of NMR techniques, most notably NOE signals between the C9a and C2 methine protons, as well as between the vinyl and C7 methine protons. It is likely that the initially formed iminium triflate **20** underwent epimerization to the more thermodynamically stable *cis*-stereoisomer **21**, in which both C9a and C2 substituents occupied pseudo-equatorial orientations in an envelope conformation. Subsequent approach of the dipolarophile to the *cis*-substituted



Scheme 4. Intermolecular dipolar azomethine ylide cycloaddition proceeds with C2 epimerization.

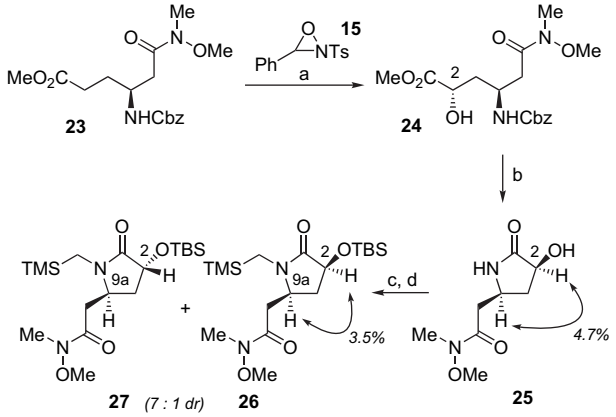
azomethine ylide corresponding to **21**, from the face opposite to the C9a and C2 substituents in a sterically governed cycloaddition, led to the formation of pyrrolizidine **22**.

Support for the rationale of C2-epimerization at the iminium stage of the reaction was obtained by in situ NMR monitoring of the O-triflation process of the *trans*-substituted vinylogous amide **19** (Scheme 5) in $CDCl_3$. Clean formation of the corresponding vinylogous iminium triflate was observed within 1 h, providing a 4:1 mixture of the *trans*- and *cis*-iminium triflates **20** and **21**, respectively. After extending the NMR reaction time to 4.5 h, further C2-epimerization occurred to provide a 1:2 ratio of **20/21**, signaling the thermodynamic preference for the *cis*-iminium triflate **21**. Unfortunately, all attempts to modify the reaction conditions to avoid C2-epimerization, or to effect C9a- or C3-epimerization via reversible β-elimination, were unsuccessful.[26] Notably, the non-epimerizeable C9a and C3 substituents in the observed cycloadduct **22** occupied the same face of the pyrrolizidine ring system; thus, it was not possible to execute the transannular Dieckmann condensation for the advancement of the synthesis to stemofoline (**1**).

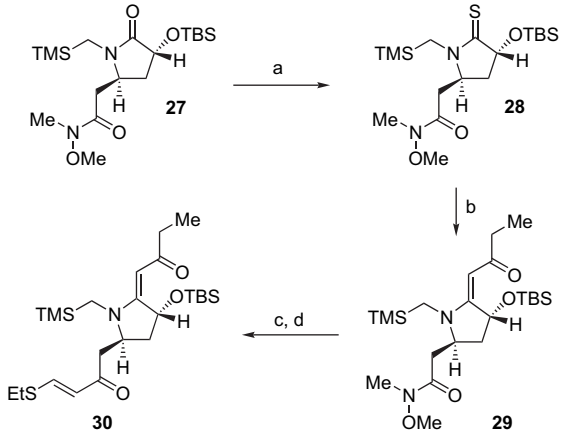


Scheme 5. C2 epimerization of iminium triflate.

Given the stereochemical impasse in the intermolecular cycloaddition approach, efforts then focused on the intramolecular cycloaddition strategy utilizing the novel vinylogous amide **11** (Scheme 2B). In this route, face-selective approach of the pendant dipolarophile in the substrate **11** would be dictated solely by the C9a-configuration irrespective of the stereoconfiguration at C2. Indeed, the success of a related intramolecular cycloaddition in our earlier model study with a simplified substrate devoid of C2-oxygenation boded well for this strategy.[13] This approach began with *N*-methoxymethyl amide **23**, available in three steps from *N*-benzyloxycarbonyl-L-glutamic acid-5-methyl ester.[13] Hydroxylation of the lithium enolate of **23** (Scheme 6) with Davis oxaziridine **15** provided the secondary alcohol **24** as a single diastereomer (57%). Hydrogenolysis of the benzyl carbamate (Pd/C, H_2) preceded spontaneous lactamization to provide **25** (94%). Selective protection of the secondary alcohol as a TBS ether (91%) was followed by N-alkylation of the lactam with (chloromethyl)trimethylsilane, which proceeded with C2 epimerization, providing a 7:1 mixture (70% overall) favoring the *trans*-lactam isomer **27** over its *cis*-counterpart **26**, whose structure was verified by the presence of a C9a−C2 methine NOE. Lactam **27** was elaborated to the (*E*)-vinylogous amide **29** by thionation with Lawesson's reagent (86%) and subsequent Eschenmoser sulfide contraction (52%, Scheme 7). The dipolarophile was installed by treatment of **29** with ethynylmagnesium chloride and trapping the



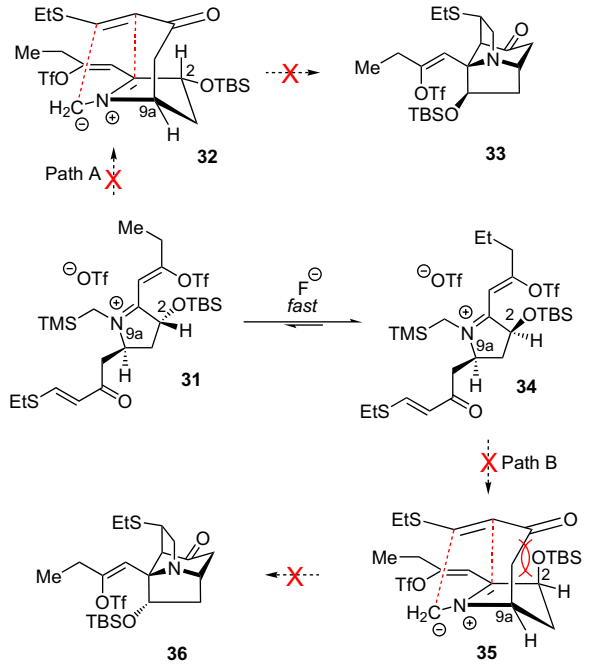
Scheme 6. (a) LHMDS, THF, −78 °C, 57%; (b) 1 atm H_2, 10% Pd/C, MeOH, 23 °C, 94%; (c) TBSCl, imidazole, DMF, 23 °C, 91%; (d) NaH, $TMSCH_2Cl$, DMF, 23 °C, 70%.



Scheme 7. (a) Lawesson's reagent, PhMe, 23 °C, 86%; (b) 1-bromo-2-butanone, 60 °C; Ph_3P, Et_3N, CH_2Cl_2, 23 °C, 52%; (c) HCCMgCl, THF, 23 °C; (d) EtSH, Et_3N, CH_2Cl_2, 23 °C, 57% (two steps).

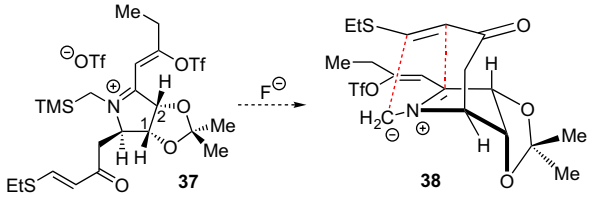
resulting reactive ynone with ethane thiol, providing the *trans*-vinylogous thioester **30** (57%, two steps), thereby setting the stage for an intramolecular azomethine ylide cycloaddition.

In this key reaction, clean formation of iminium triflate **31** was observed by ^{1}H NMR upon treatment of vinylogous amide **30** with Tf_2O; however, only an intractable mixture of products was obtained after addition of TBAT. Based on analogy to the C2 epimerization of iminium triflate **20** (cf. Scheme 4), it is likely that fluoride anion, prior to desilylating iminium triflate **31**, acted as a general base to effect C2 epimerization, resulting in a rapid equilibrium favoring iminium **34**, in which the C9a and C2 substituents would both occupy pseudo-equatorial positions in the envelope conformation. The observed lack of productive cycloaddition might arise from the absence of any appreciable quantity of ylide **32** that could react to form the desired cycloadduct **33** (Scheme 8, path A). Rather, the reaction was dominated by the *cis*-iminium **34**, kinetically favoring decomposition pathways over cycloaddition. This outcome could be rationalized by an energetically disfavored cycloaddition transition state **35** (Scheme 8, path B), incorporating severe C9a–C2 1,3-diaxial interactions, giving way to other, as yet unidentified, unproductive reaction manifolds.



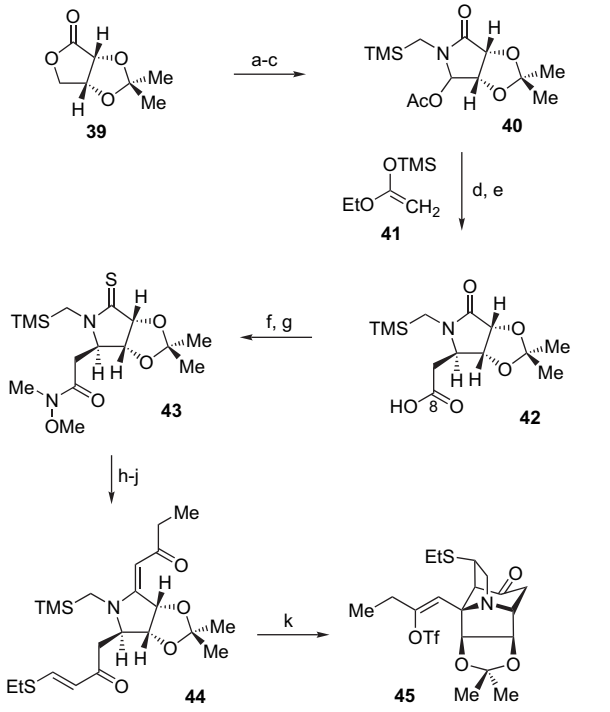
Scheme 8. C2 epimerization of iminium triflate.

Given the likelihood of C2-epimerization in **31** imparting a detrimental effect on the intramolecular cycloaddition strategy, a modification of this approach was explored, employing a cycloaddition substrate incapable of C2-epimerization. In this context, iminium triflate **37** (Scheme 9), in which the C1 and C2 oxygen substituents are tethered as part of a *cis*-fused isopropylidene ketal, was pursued. In this intermediate, C2 epimerization would be prohibited as a result of formation of a high-energy *trans*-fused [3.3.0]-bicyclo system.



Scheme 9. Proposed dipolar azomethine ylide cycloaddition.

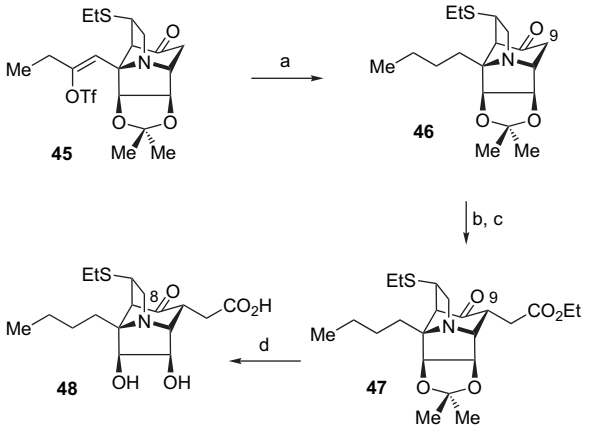
Synthesis of the newly designed cycloaddition substrate began with the treatment of the commercially available (−)-2,3-*O*-isopropylidine-D-erythronolactone (**39**) with (trimethylsilyl)-methyl amine (97%, Scheme 10). Parikh–Doering oxidation of the resulting primary alcohol furnished a hemiaminal, which was acetylated to afford aminal **40** (69%, two steps). Lewis acid-promoted Mannich reaction between aminal **40** and the trimethylsilylketene acetal of ethyl acetate (**41**, 72%) was followed by hydrolysis of the resulting ester to provide carboxylic acid **42** (96%). Thionation of the lactam functionality within **42** was accomplished by heating in the presence of Lawesson's reagent (95%), and the C8-carboxyl group in the resulting product was then converted to the corresponding *N*-methoxy-*N*-methyl amide **43** (62%). Eschenmoser sulfide contraction (81%) and then treatment with ethynylmagnesium bromide



Scheme 10. (a) $TMSCH_2NH_3Cl$, Et_3N, THF, 70 °C, 97%; (b) $SO_3\cdot Py$, Et_3N, DMSO, 23 °C; (c) Ac_2O, pyridine, 23 °C, 69% (two steps); (d) TMSOTf, CH_2Cl_2, 23 °C, 72%; (e) LiOH, THF, H_2O, 23 °C, 96%; (f) Lawesson's reagent, PhMe, 65 °C, 95%; (g) MeONHMe·HCl, EDC, Et_3N, CH_2Cl_2, 23 °C, 62%; (h) 1-bromo-2-butanone; Ph_3P, Et_3N, CH_3CN, 23 °C, 81%; (i) HCCMgBr, THF, 23 °C; (j) EtSH, Et_3N, CH_2Cl_2, 23 °C, 58% (two steps); (k) Tf_2O, TBAT, $CHCl_3$, −45 to 23 °C, 71%.

and ethane thiol (58%, two steps) installed the required functionality for the proposed intramolecular [3+2] azomethine ylide cycloaddition. In this event, sequential treatment of **44** with triflic anhydride and TBAT provided the desired polycyclic alkaloid **45** in 71% yield. This result comprises the first non-racemic synthesis of the fully oxygenated bridged pyrrolizidine core of the stemofoline alkaloids.

Further advancement of the cycloadduct **45** (Scheme 11) involved reduction of its enol triflate functionality under a hydrogen atmosphere in the presence of Pd/C to provide pyrrolizidine **46** (89%), which contains the saturated butyl side chain present in (+)-stemofoline (**1**). Installation of a two-carbon functionality at the equatorial position of C9 was accomplished by enolate alkylation of ketone **46** with ethyl iodoacetate, followed by C9 equilibration (DBU, heat), to afford the ethyl ester **47** (58%, two steps). Treatment of **47** with aqueous hydrochloric acid effected deprotection of the isopropylidene group and hydrolysis of the ester (96%), providing a versatile intermediate **48** to explore strategies for butenolide construction and C8 ketal closure en route to the stemofoline alkaloids.



Scheme 11. (a) 1 atm H_2, 10% Pd/C, MeOH, 23 °C, 89%; (b) LDA, ICH_2CO_2Et, THF, HMPA, 0 °C; (c) DBU, PhMe, 80 °C, 58% (two steps); (d) 2.5 M HCl, THF, 60 °C, 96%.

3. Conclusion

A key observation regarding the dependence of α-stereochemistry in the azomethine ylide generation and intramolecular dipolar cycloaddition of vinylogous amide **44** led to the development of a successful non-racemic synthesis of the bridged pyrrolizidine core of the stemofoline alkaloids.

4. Experimental section

4.1. General

All reactions were performed in flame-dried modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe. Organic solutions were concentrated by rotary evaporation below 30 °C. Flash column chromatography was performed employing 230–400 mesh silica gel. Thin-layer chromatography (analytical and preparative) was performed using glass plates pre-coated to a depth of 0.25 mm with 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Infrared (IR) spectra were obtained using a Perkin Elmer Spectrum BX spectrophotometer or a Bruker Tensor 27 referenced to a polystyrene standard. Data are presented as the frequency of absorption (cm^{-1}). Proton and carbon-13 nuclear magnetic resonance (^1H NMR or ^{13}C NMR) spectra were recorded on a Varian 400, a Varian 500, Varian Inova 500 NMR, or a Bruker Avance III spectrometer; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the residual protium in the NMR solvent ($CHCl_3$: δ 7.26 for ^1H NMR, δ 77.16 for ^{13}C NMR; CD_3OD: δ 3.30 for ^1H NMR, δ 49.00 for ^{13}C NMR). Data are presented as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, br d=broad doublet, t=triplet, m=multiplet and/or multiple resonances), coupling constant in hertz (Hz), integration, assignment.

4.2. Dimethyl 3-(benzyloxycarbonylamino)hexanedioate (*14*)

To a stirred solution of 2-benzyloxycarbonylamino-pentanedioic acid-5-methyl ester (**13**) (4.45 g, 15.1 mmol, 1.0 equiv) and triethylamine (2.31 mL, 16.5 mmol, 1.1 equiv) in tetrahydrofuran (80 mL) at −10 °C was added via syringe ethyl chloroformate (1.60 mL, 16.5 mmol, 1.1 equiv). The white

suspension was stirred at −10 °C for 1 h before the addition of diazomethane (0.58 M solution in diethyl ether, 80 mL, 47 mmol, 3.1 equiv). The bright yellow suspension was stirred at −10 °C for 1 h and then 23 °C for 3 h. The reaction mixture was then diluted with diethyl ether (600 mL) and washed with water (1×150 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel flash chromatography (50% hexanes in ethyl acetate) provided 4-benzyloxycarbonylamino-6-diazo-5-oxo-hexanoic acid methyl ester (4.21 g, 87%) as a yellow solid. R_f=0.43 (50% hexanes in ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.37−7.30 (m, 5H, Ph), 5.60 (d, 1H, J=9.2 Hz, N*H*), 5.50 (br s, 1H, C*H*N_2), 5.09 (s, 2H, CH_2Ph), 4.31 (m, 1H, CH_2CH_2CH-C(O)CHN_2), 3.67 (s, 3H, CO_2CH_3), 2.46 (m, 1H, $CH_2CO_2CH_3$), 2.39 (m, 1H, $CH_2CO_2CH_3$), 2.16 (m, 1H, CH_2CH_2CHC-(O)CHN_2), 1.85 (m, 1H, CH_2CH_2CHC(O)CHN_2); FTIR (neat film, NaCl) 3327, 2953, 2110, 1731, 1640, 1525, 1440, 1336 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{15}H_{18}N_3O_5$ (MH^+) 320.1246, found 320.1247. Silver acetate (320 mg, 1.92 mmol, 0.20 equiv) was added to a stirred solution of 4-benzyloxycarbonyl-amino-6-diazo-5-oxo-hexanoic acid methyl ester (3.07 g, 9.61 mmol, 1.0 equiv) in dry methanol (50 mL). The resulting brown suspension was stirred at room temperature for 12 h. The reaction mixture was then filtered through Celite and the filtrate concentrated. Purification by silica gel flash chromatography (40% ethyl acetate in hexanes) afforded **14** (2.83 g, 91%) as a white powder. R_f=0.48 (50% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.29 (m, 5H, Ph), 5.32 (d, 1H, J=9.2 Hz, N*H*), 5.09 (m, 2H, CH_2Ph), 4.01 (m, 1H, CH_2-C*H*NHCbz), 3.67 (s, 3H, CO_2CH_3), 3.66 (s, 3H, CO_2CH_3), 2.58 (t, 2H, J=4.6 Hz, $CH_2CO_2CH_3$), 2.41 (t, 2H, J=7.2 Hz, $CH_2CO_2CH_3$), 1.89 (m, 2H, $CH_2CH_2CO_2CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 172.0, 156.1, 136.6, 128.7, 128.4, 128.3, 67.4, 66.9, 52.0, 47.9, 39.1, 31.0, 29.5; FTIR (neat film, NaCl) 3350, 2953, 1737, 1691, 1530, 1438, 1245, 1056, 740, 699 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{16}H_{22}N_1O_6$ (MH^+) 324.1447, found 324.1446.

4.3. 4-Benzyloxycarbonylamino-2-hydroxy-hexanedioic acid dimethyl ester (*16*)

A stirred solution of **14** (776 mg, 2.40 mmol, 1.0 equiv) and 3-phenyl-2-(toluene-4-sulfonyl)oxaziridine (**15**) (990 mg, 3.60 mmol, 1.5 equiv) in dry tetrahydrofuran (30 mL) at −78 °C was added dropwise via cannula to a −78 °C solution of lithium bis(trimethylsilyl)amide (1.20 g, 7.20 mmol, 3.0 equiv) in tetrahydrofuran (20 mL). The bright yellow solution was then stirred at −78 °C for 30 min and then quenched by the addition of dry methanol (10 mL). The resulting solution was then warmed to room temperature, diluted with diethyl ether (500 mL), and washed with 1.0 N aqueous hydrochloric acid (1×100 mL) and saturated aqueous sodium bicarbonate (1×100 mL). The organic layer was then separated, dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel flash chromatography (33% hexanes in ethyl acetate) provided **16** (419 mg, 52%) as a colorless oil. R_f=0.49 (33% hexanes in ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.29 (m, 5H, Ph), 5.69 (br d, 1H, J=9.3 Hz, N*H*), 5.10 (br s, 2H, CH_2Ph), 4.28 (br m, 2H, C*H*OH and C*H*NHCbz), 3.77 (s, 3H, CO_2CH_3), 3.68 (s, 3H, CO_2CH_3), 3.54 (br d, 1H, J=4.7 Hz, O*H*), 2.66 (t, 2H, J=5.7 Hz, $CH_2CO_2CH_3$), 2.12 (ddd, 1H, J=14.0, 10.2, 2.6 Hz, CH_2CHNHCbz), 1.77 (ddd, 1H, J=14.2, 10.9, 3.7 Hz, CH_2CHNHCbz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 172.1, 156.8, 136.6, 128.8, 128.5, 128.4, 68.1, 67.3, 52.8, 52.1, 45.3, 38.8, 38.7; FTIR (neat film, NaCl) 3368, 2954, 1734, 1732, 1692, 1531, 1439, 1251, 1217, 1111, 1056, 741 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{16}H_{22}N_1O_7$ (MH^+) 340.1396, found 340.1395.

4.4. [4-(tert-Butyl-dimethyl-silanyloxy)-5-oxo-pyrrolidin-2-yl]-acetic acid methyl ester (*17*)

A 100-mL round bottom flask containing **16** (419 mg, 1.23 mmol) and 10% palladium on carbon (ca. 20 mg) in methanol (20 mL) was charged with hydrogen via balloon, and the mixture was stirred at room temperature under the hydrogen atmosphere for 2 h. The reaction mixture was then filtered through Celite and concentrated. The crude amino alcohol was then dissolved in pyridine (20 mL) and heated to 100 °C to effect lactamization. After 24 h, the solution was cooled to room temperature, and *tert*-butyldimethylsilyl chloride (445 mg, 2.96 mmol, 2.4 equiv) and imidazole (419 mg, 6.15 mmol, 5.0 equiv) were added. The solution was stirred at room temperature for 4 h and concentrated in vacuo. Purification by silica gel flash chromatography (33% hexanes in ethyl acetate) provided **17** (336 mg, 95%) as a white solid. R_f=0.40 (40% hexanes in ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (br s, 1H, N*H*), 4.25 (t, 1H, J=7.5 Hz, CH_2CHOTBS), 3.84 (m, 1H, CH_2CHN), 3.71 (s, 3H, CO_2CH_3), 2.58 (m, 3H, $CH_2CO_2CH_3$ and CH_2CHOTBS), 1.66 (dt, 1H, J=12.9, 7.3 Hz, CH_2CHOTBS), 0.91 (s, 9H, TBS *tert*-butyl), 0.16 (s, 3H, TBS methyl), 0.14 (s, 3H, TBS methyl); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 172.1, 70.3, 52.2, 46.9, 41.2, 37.6, 26.0, 18.3, −4.34, −5.06; FTIR (neat film, NaCl) 3234, 2949, 1738, 1694, 1473, 1391, 1296, 1252, 1162, 1056, 840, 777 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{13}H_{26}N_1O_4Si_1$ (MH^+) 288.1631, found 288.1632.

4.5. [4-(tert-Butyl-dimethyl-silanyloxy)-5-oxo-1-trimethylsilanylmethyl-pyrrolidin-2-yl]-acetic acid methyl ester (*18*)

To a stirred solution of **17** (853 mg, 2.97 mmol, 1.0 equiv) in dry dimethylformamide (8 mL) was added sodium hydride (60% suspension in mineral oil, 131 mg, 3.26 mmol, 1.1 equiv) and the resulting suspension was stirred at room temperature for 1 h. Chloromethyltrimethylsilane (1.20 mL, 8.91 mmol, 3.0 equiv) was added and the resulting suspension was stirred for an additional 3 h at room temperature. The reaction mixture was diluted with deionized water (40 mL) and extracted with diethyl ether (1×200 mL). The organic extracts were dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel flash chromatography (20% ethyl acetate in hexanes) provided **18** (666 mg, *trans*-isomer only, 60%) as a

colorless oil. R_f=0.60 (33% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (dd, 1H, J=7.4, 4.7 Hz, $CH_2CHOTBS$), 3.80 (ddt, 1H, J=9.9, 7.3, 4.5 Hz, CH_2CHN), 3.72 (s, 3H, CO_2CH_3), 3.20 (d, 1H, J=15.4 Hz, $TMSCH_2N$), 2.86 (dd, 1H, J=15.8, 4.4 Hz, $CH_2CO_2CH_3$), 2.49 (dd, 1H, J=15.7, 9.9 Hz, $CH_2CO_2CH_3$), 2.46 (dt, 1H, J=13.4, 7.3 Hz, $CH_2CHOTBS$), 2.33 (d, 1H, J=15.3 Hz, $TMSCH_2N$), 1.68 (dt, 1H, J=13.4, 4.6 Hz, $CH_2CHOTBS$), 0.90 (s, 9H, TBS *tert*-butyl), 0.15 (s, 3H, TBS methyl), 0.14 (s, 3H, TBS methyl), 0.086 (s, 9H, TMS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 171.6, 70.5, 54.4, 52.1, 38.9, 35.8, 32.3, 25.9, 18.4, −1.28, −4.31, −5.05; FTIR (neat film, NaCl) 2954, 1740, 1699, 1437, 1363, 1324, 1251, 1199, 1152, 1127, 983, 840, 780 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{17}H_{36}N_1O_4Si_2$ (MH^+) 374.2183, found 374.2184.

4.6. [4-(tert-Butyl-dimethyl-silanyloxy)-5-(2-oxo-butylidene)-1-trimethylsilanyl-methyl-pyrrolidin-2-yl]-acetic acid methyl ester (**19**)

To a stirred solution of **18** (666 mg, 1.78 mmol, 1.0 equiv) in dry toluene (10 mL) at room temperature was added Lawesson's reagent (397 mg, 0.981 mmol, 0.55 equiv). The resulting yellow suspension was stirred at 65 °C for 1 h. The reaction mixture was then concentrated in vacuo. Purification by silica gel flash chromatography (16% ethyl acetate in hexanes) provided [4-(*tert*-butyl-dimethyl-silanyloxy)-5-thioxo-1-trimethylsilanyl-methyl-pyrrolidin-2-yl]-acetic acid methyl ester (657 mg, 95%) as a colorless oil. R_f=0.59 (20% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (dd, 1H, J=6.6, 2.9 Hz, $CH_2CHOTBS$), 4.10 (dddd, 1H, J=9.8, 6.9, 4.1, 2.9 Hz, CH_2CHN), 3.94 (d, 1H, J=14.7 Hz, $TMSCH_2N$), 3.73 (s, 3H, CO_2CH_3), 2.90 (dd, 1H, J=15.9, 4.1 Hz, $CH_2CO_2CH_3$), 2.83 (d, 1H, J=14.7 Hz, $TMSCH_2N$), 2.71 (dd, 1H, J=15.9, 9.8 Hz, $CH_2CO_2CH_3$), 2.43 (dt, 1H, J=13.5, 6.9 Hz, $CH_2CHOTBS$), 1.79 (dt, 1H, J=13.5, 2.9 Hz, $CH_2CHOTBS$), 0.90 (s, 9H, TBS *tert*-butyl), 0.20 (s, 3H, TBS methyl), 0.18 (s, 3H, TBS methyl), 0.14 (s, 9H, TMS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.8, 171.3, 80.0, 62.8, 52.3, 38.7, 38.4, 36.7, 25.9, 18.3, −0.63, −3.95, −5.03; FTIR (neat film, NaCl) 2953, 1740, 1492, 1437, 1363, 1319, 1251, 1199, 1153, 1129, 1091, 842, 780 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{17}H_{36}N_1O_3S_1Si_2$ (MH^+) 390.1954, found 390.1955. To a stirred solution of [4-(*tert*-butyl-dimethyl-silanyloxy)-5-thioxo-1-trimethylsilanylmethyl-pyrrolidin-2-yl]-acetic acid methyl ester (96.2 mg, 0.247 mmol, 1.0 equiv) in dichloromethane (2 mL) was added 1-bromo-2-butanone (30 μL, 0.27 mmol, 1.1 equiv). The colorless solution was then concentrated in vacuo and the resulting oil was heated at 60 °C for 20 min. The resulting white solid was dissolved in dichloromethane (2 mL), and triphenylphosphine (71.1 mg, 0.271 mmol, 1.1 equiv) and triethylamine (40 μL, 0.27 mmol, 1.1 equiv) were added at room temperature. The resulting yellow solution was then stirred for 1 h at room temperature and concentrated. Purification by silica gel flash chromatography (13% ethyl acetate in benzene) provided **19** (75.3 mg, 71%, (*E*)-isomer only) as a white solid. R_f=0.32 (15% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 6.01 (d, 1H, J=5.2 Hz, $CH_2CHOTBS$), 4.83 (s, 1H, vinyl H), 3.67 (ddt, 1H, J=9.4, 7.4, 4.4 Hz, CH_2CHN), 3.34 (s, 3H, CO_2CH_3), 2.88 (dd, 1H, J=15.7, 9.4 Hz, $CH_2CO_2CH_3$), 2.68 (dd, 1H, J=15.8, 4.4 Hz, $CH_2CO_2CH_3$), 2.45 (d, 1H, J=15.7 Hz, $TMSCH_2N$), 2.41 (q, 2H, J=7.4 Hz, CH_2CH_3), 2.28 (d, 1H, J=15.7 Hz, $TMSCH_2N$), 1.75 (m, 2H, $CH_2CHOTBS$), 1.27 (t, 3H, J=7.4 Hz, CH_2CH_3), 1.01 (s, 9H, TBS *tert*-butyl), 0.51 (s, 3H, TBS methyl), 0.40 (s, 3H, TBS methyl), −0.078 (s, 9H, TMS); ^{13}C NMR (126 MHz, C_6D_6) δ 195.2, 172.1, 163.3, 89.9, 72.4, 61.6, 51.5, 39.2, 37.8, 37.2, 36.1, 26.6, 18.8, 10.4, −0.79, −3.69, −5.00; FTIR (neat film, NaCl) 2929, 2856, 1739, 1651, 1564, 1437, 1371, 1314, 1251, 1209, 1126, 1098, 853, 780 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{21}H_{42}N_1O_4Si_2$ (MH^+) 428.2652, found 428.2651.

4.7. 7-(tert-Butyl-dimethyl-silanyloxy)-5-methoxycarbonyl-methyl-7a-(2-trifluoro-methanesulfonyloxy-but-1-enyl)-hexahydro-pyrrolizine-1-carboxylic acid methyl ester (**22**)

To a stirred solution of **19** (9.2 mg, 0.022 mmol, 1.0 equiv) in dichloromethane (500 μL) at room temperature was added via syringe trifluoromethanesulfonic anhydride (4.0 μL, 0.024 mmol, 1.1 equiv). The resulting yellow solution was stirred for 15 min at room temperature before the addition of methyl acrylate (20 μL, 0.22 mmol, 10.0 equiv) and tetrabutylammonium triphenyldifluorosilicate (12.8 mg, 0.0237 mmol, 1.1 equiv). The resulting dark red solution was stirred at room temperature for 1 h. The reaction mixture was then concentrated in vacuo. Purification by silica gel flash chromatography (17% ethyl acetate in hexanes) provided **22** (6.8 mg, 55%, (*Z*)-isomer only) as a colorless oil. R_f=0.50 (17% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 6.08 (br s, 1H, vinyl H), 4.17 (dd, 1H, J=11.2, 6.0 Hz, $CH_2CHOTBS$), 3.39 (s, 3H, CO_2CH_3), 3.36 (s, 3H, CO_2CH_3), 3.19 (td, 1H, J=12.1, 5.1 Hz, CH_2N), 3.10 (m, 1H, CH_2CHN), 2.90 (dd, 1H, J=16.5, 5.3 Hz, $CH_2CO_2CH_3$), 2.80 (dd, 1H, J=12.2, 6.1 Hz, $CHCO_2CH_3$), 2.66 (ddd, 1H, J=12.1, 7.2, 1.0 Hz, CH_2N), 2.62 (dd, 1H, J=16.5, 8.5 Hz, $CH_2CO_2CH_3$), 2.24 (m, 1H, $CH_2CHOTBS$), 2.13 (m, 1H, CH_2CH_3), 2.00 (m, 1H, CH_2CH_3), 1.92 (m, 1H, CH_2CHN), 1.50 (m, 1H, $CH_2CHOTBS$), 1.48 (m, 1H, CH_2CHN), 0.91 (s, 9H, TBS *tert*-butyl), 0.86 (t, 3H, J=7.3 Hz, CH_2CH_3), 0.066 (s, 3H, TBS methyl), −0.028 (s, 3H, TBS methyl); FTIR (neat film, NaCl) 2957, 1736, 1438, 1413, 1260, 1202, 1144, 1033, 978, 884, 779 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{23}H_{39}N_1O_8F_3S_1Si_1$ (MH^+) 574.2118, found 574.2119.

4.8. Iminium triflates **20** and **21**

To a stirred solution of **19** (19.3 mg, 0.0450 mmol, 1.0 equiv) in $CDCl_3$ (1 mL, freshly distilled from CaH_2 under N_2 at atmospheric pressure) at room temperature was added via syringe trifluoromethanesulfonic anhydride (9.0 μL, 0.050 mmol, 1.1 equiv). The resulting pale orange solution was stirred for 1 h at room temperature. Examination of the reaction mixture by ^{1}H NMR revealed both **20** and **21** (>95% conversion, as

a 4:1 mixture of **20/21**), each formed as the (*Z*)-isomer with respect to the enol triflate double bond. The solution was then stirred at room temperature for an additional 4.5 h. Examination of the reaction mixture by ^{1}H NMR revealed both **20** and **21** (>95% conversion, as a 1:2 mixture of **20/21**). *Iminium triflate **20***: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (br s, 1H, vinyl H), 5.55 (dd, 1H, J=6.9, 3.2 Hz, $CH_2CHOTBS$), 4.61 (ddt, 1H, J=9.1, 7.5, 3.8 Hz, CH_2CHN), 4.29 (d, 1H, J=14.5 Hz, $TMSCH_2N$), 3.78 (s, 3H, CO_2CH_3), 3.40 (d, 1H, J=14.5 Hz, $TMSCH_2N$), 3.23 (dd, 1H, J=16.9, 4.2 Hz, $CH_2CO_2CH_3$), 2.91 (dd, 1H, J=17.0, 9.1 Hz, $CH_2CO_2CH_3$), 2.86 (dt, 1H, J=13.9, 7.5 Hz, $CH_2CHOTBS$), 2.73 (m, 1H, CH_2CH_3), 2.61 (m, 1H, CH_2CH_3), 2.05 (dt, 1H, J=13.8, 3.3 Hz, $CH_2CHOTBS$), 1.32 (t, 3H, J=7.3 Hz, CH_2CH_3), 0.89 (s, 3H, TBS methyl), 0.88 (s, 9H, TBS *tert*-butyl), 0.86 (s, 3H, TBS methyl), 0.26 (s, 9H, TMS). *Iminium triflate **21***: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (br s, 1H, vinyl H), 5.41 (t, 1H, J=7.6 Hz, $CH_2CHOTBS$), 4.89 (dtd, 1H, J=8.9, 7.5, 4.8 Hz, CH_2CHN), 4.18 (d, 1H, J=14.7 Hz, $TMSCH_2N$), 3.77 (s, 3H, CO_2CH_3), 3.39 (d, 1H, J=14.7 Hz, $TMSCH_2N$), 3.11 (dd, 1H, J=16.5, 4.8 Hz, $CH_2CO_2CH_3$), 2.86 (dt, 1H, J=12.9, 7.5 Hz, $CH_2CHOTBS$), 2.78 (dd, 1H, J=16.5, 8.9 Hz, $CH_2CO_2CH_3$), 2.77 (m, 1H, CH_2CH_3), 2.62 (m, 1H, CH_2CH_3), 1.89 (dt, 1H, J=12.9, 7.8 Hz, $CH_2CHOTBS$), 1.30 (t, 3H, J=7.4 Hz, CH_2CH_3), 1.01 (s, 3H, TBS methyl), 0.89 (s, 9H, TBS *tert*-butyl), 0.85 (s, 3H, TBS methyl), 0.31 (s, 9H, TMS).

4.9. 4-Benzyloxycarbonylamino-2-hydroxy-5-(methoxy-methyl-carbamoyl) pentanoic acid methyl ester (*24*)

To a stirred solution of **23** (2.51 g, 7.36 mmol, 1.0 equiv) and 3-phenyl-2-(toluene-4-sulfonyl)-oxaziridine (**15**) (3.04 g, 11.0 mmol, 1.5 equiv) in dry tetrahydrofuran (80 mL) at −78 °C was added dropwise via cannula a cold (−78 °C) solution of lithium bis(trimethylsilyl)amide (2.71 g, 16.2 mmol, 2.2 equiv) in tetrahydrofuran (80 mL). The bright yellow solution was then stirred at −78 °C for 20 min and then quenched by the cannula addition of a solution of camphor sulfonic acid (6.67 g, 29.4 mmol, 4.0 equiv) in tetrahydrofuran (40 mL). The resulting solution was then warmed to room temperature, diluted with diethyl ether (500 mL), and washed with 1.0 N aqueous hydrochloric acid (1×100 mL) and saturated aqueous sodium bicarbonate (1×100 mL). The organic layer was then separated, dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel flash chromatography (ethyl acetate) provided **24** (1.50 g, 57%) as a white solid. R_f=0.45 (ethyl acetate); $[\alpha]_D^{24}$ −16.5 (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.41−7.30 (m, 5H, Ph), 6.13 (br d, 1H, J=8.6 Hz, N*H*), 5.10 (br s, 2H, CH_2Ph), 4.28 (br m, 2H, CH_2CHOH and $CH_2CHNHCbz$), 3.76 (s, 3H, $NOCH_3$), 3.66 (s, 3H, CO_2CH_3), 3.16 (s, 3H, NCH_3), 2.87 (br d, 1H, J=15.3 Hz, $CH_2CHNHCbz$), 2.69 (br dd, 1H, J=16.3, 4.4 Hz, $CH_2CHNHCbz$), 2.21 (t, 1H, J=11.8 Hz, CH_2CHOH), 1.75 (br m, 1H, CH_2CHOH); ^{13}C NMR ($CDCl_3$) δ 174.7, 172.3, 157.0, 136.6, 128.7, 128.3, 128.2, 68.2, 67.1, 61.5, 52.6, 45.3, 39.1, 35.8, 32.0; FTIR (neat film, NaCl) 3340, 2953, 1736, 1719, 1642, 1528, 1438, 1390, 1254, 1111, 1053, 996, 741 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{17}H_{25}N_2O_7$ (MH^+) 369.1662, found 369.1663.

4.10. 2-(4-Hydroxy-5-oxo-pyrrolidin-2-yl)-N-methoxy-N-methyl-acetamide (*25*)

A suspension of **24** (1.25 g, 3.39 mmol) and 10% palladium on carbon (ca. 200 mg) in methanol (50 mL) was charged with hydrogen via balloon, and the mixture was stirred at room temperature under the hydrogen atmosphere for 1 h. The reaction mixture was then filtered through Celite and concentrated at 35 °C using a rotary evaporator. Purification by silica gel flash chromatography (10% methanol in ethyl acetate) provided **25** (642 mg, 94%) as a white solid. R_f=0.21 (10% methanol in ethyl acetate); $[\alpha]_D^{24}$ +4.3 (*c* 1.24, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (br s, 1H, N*H*), 4.33 (t, 1H, J=8.6 Hz, CH_2CHOH), 4.15 (br s, 1H, O*H*), 3.89 (br m, 1H, CH_2CHN), 3.69 (s, 3H, $NOCH_3$), 3.18 (s, 3H, NCH_3), 2.86 (br d, 1H, J=16.1 Hz, $CH_2C(O)N(CH_3)OCH_3$), 2.66 (br m, 1H, CH_2CHOH), 2.54 (dd, 1H, J=16.8, 9.7 Hz, $CH_2C(O)N(CH_3)OCH_3$), 1.70 (dt, 1H, J=12.9, 8.3 Hz, CH_2CHOH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 172.2, 89.3, 61.2, 52.7, 38.5, 36.1, 31.4; FTIR (neat film, NaCl) 3391, 2930, 1698, 1643, 1434, 1393, 1304, 1181, 1118, 993 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_8H_{15}N_2O_4$ (MH^+) 203.1032, found 203.1033.

4.11. Lactams *26* and *27*

To a stirred solution of **25** (642 mg, 3.17 mmol, 1.0 equiv) and imidazole (1.08 g, 15.9 mmol, 5.0 equiv) in anhydrous dimethylformamide (30 mL) at room temperature was added *tert*-butyldimethylsilyl chloride (957 mg, 6.35 mmol, 2.0 equiv). The resulting solution was stirred at room temperature for 24 h. The reaction mixture was then diluted with deionized water (250 mL) and extracted with diethyl ether (2×300 mL). The organic extracts were then combined, dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel flash chromatography (ethyl acetate) provided 2-[4-(*tert*-butyl-dimethylsilanyloxy)-5-oxo-pyrrolidin-2-yl]-*N*-methoxy-*N*-methyl acetamide (913 mg, 91%) as a colorless oil. R_f=0.43 (ethyl acetate); $[\alpha]_D^{24}$ +15.3 (*c* 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (br d, 1H, J=8.6 Hz, N*H*), 4.23 (t, 1H, J=7.6 Hz, $CH_2CHOTBS$), 3.83 (br m, 1H, CH_2CHN), 3.65 (s, 3H, $NOCH_3$), 3.15 (s, 3H, NCH_3), 2.76 (dd, 1H, J=16.9, 2.6 Hz, $CH_2C(O)N(CH_3)OCH_3$), 2.56 (m, 2H, $CH_2C(O)N(CH_3)OCH_3$ and $CH_2CHOTBS$), 1.66 (dt, 1H, J=13.0, 7.2 Hz, $CH_2CHOTBS$), 0.88 (s, 9H, TBS *tert*-butyl), 0.13 (s, 3H, TBS methyl), 0.11 (s, 3H, TBS methyl); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 172.1, 70.3, 61.4, 46.9, 39.4, 37.6, 32.1, 25.9, 18.4, −4.4, −5.1; FTIR (neat film, NaCl) 3293, 2954, 1715, 1660, 1472, 1390, 1300, 1252, 1151, 1054, 997, 861, 839 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{14}H_{29}N_2O_4Si_1$ (MH^+) 317.1897, found 317.1898. To a stirred solution of 2-[4-(*tert*-butyl-dimethylsilanyloxy)-5-oxo-pyrrolidin-2-yl]-*N*-methoxy-*N*-methyl acetamide (215 mg, 0.679 mmol, 1.0 equiv) in dry dimethylformamide (6 mL) was added sodium hydride (60% suspension in mineral oil, 30.0 mg, 0.747 mmol,

1.1 equiv) and the resulting suspension was stirred at room temperature for 1.5 h. Chloromethyltrimethylsilane (290 μL, 2.04 mmol, 3.0 equiv) was added and the resulting suspension was stirred for an additional 18 h at room temperature. The reaction mixture was diluted with deionized water (50 mL) and extracted with diethyl ether (1×500 mL). The organic extracts were dried over magnesium sulfate, filtered, and concentrated. Purification by silica gel flash chromatography (40% ethyl acetate in hexanes) provided **26** and **27** (191 mg as a separable 7:1 mixture favoring **27**, 70% total) as colorless oils. *Lactam **26***: R_f=0.52 (50% hexanes in ethyl acetate); $[\alpha]_D^{24}$ +28.2 (*c* 1.18, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (t, 1H, *J*=7.2 Hz, $CH_2CHOTBS$), 4.00 (ddt, 1H, *J*=9.9, 6.9, 3.6 Hz, CH_2CHN), 3.69 (s, 3H, $NOCH_3$), 3.21 (d, 1H, *J*=15.2 Hz, $TMSCH_2N$), 3.19 (s, 3H, NCH_3), 2.82 (dd, 1H, *J*=15.4, 3.5 Hz, $CH_2C(O)N(CH_3)OCH_3$), 2.36 (dd, 1H, *J*=15.4, 9.9 Hz, $CH_2C(O)N(CH_3)OCH_3$), 2.29 (d, 1H, *J*=15.2 Hz, $TMSCH_2N$), 2.14 (dt, 1H, *J*=13.1, 6.9 Hz, $CH_2CHOTBS$), 2.07 (ddd, 1H, *J*=13.2, 7.5, 3.5 Hz, $CH_2CHOTBS$), 0.89 (s, 9H, TBS *tert*-butyl), 0.14 (s, 3H, TBS methyl), 0.13 (s, 3H, TBS methyl), 0.10 (s, 9H, TMS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 171.4, 69.9, 61.5, 53.8, 41.8, 36.2, 35.6, 32.3, 26.0, 18.5, −1.32, −4.23, −4.91; FTIR (neat film, NaCl) 2954, 1697 (C═O), 1664 (C═O), 1462, 1418, 1388, 1362, 1250, 1172, 1114, 1002, 856, 840, 779 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{18}H_{39}N_2O_4Si_2$ (MH^+) 403.2448, found 403.2449. *Lactam **27***: R_f=0.67 (50% hexanes in ethyl acetate); $[\alpha]_D^{24}$ −8.1 (*c* 3.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (dd, 1H, *J*=7.4, 4.4 Hz, $CH_2CHOTBS$), 3.91 (ddt, 1H, *J*=9.8, 7.0, 4.0 Hz, CH_2CHN), 3.68 (s, 3H, $NOCH_3$), 3.20 (d, 1H, *J*=15.3 Hz, $TMSCH_2N$), 3.19 (s, 3H, NCH_3), 2.95 (dd, 1H, *J*=16.2, 3.8 Hz, $CH_2C(O)N(CH_3)OCH_3$), 2.63, (dd, 1H, *J*=16.2, 9.8 Hz, $CH_2C(O)N(CH_3)OCH_3$), 2.49 (dt, 1H, *J*=14.3, 7.5 Hz, $CH_2CHOTBS$), 2.35 (d, 1H, *J*=15.3 Hz, $TMSCH_2N$), 1.65 (dt, 1H, *J*=13.5, 4.1 Hz, $CH_2CHOTBS$), 0.89 (s, 9H, TBS *tert*-butyl), 0.14 (s, 3H, TBS methyl), 0.13 (s, 3H, TBS methyl), 0.081 (s, 9H, TMS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 171.9, 70.7, 61.5, 54.4, 42.0, 36.7, 36.1, 32.4, 25.9, 18.4, −1.28, −4.35, −4.99; FTIR (neat film, NaCl) 2954, 1698, 1667, 1464, 1417, 1388, 1361, 1250, 1173, 1116, 1004, 841, 780 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{18}H_{39}N_2O_4Si_2$ (MH^+) 403.2448, found 403.2449.

*4.12. 2-[4-(tert-Butyl-dimethylsilanyloxy)-5-thioxo-1-trimethylsilanylmethyl-pyrrolidin-2-yl]-N-methoxy-N-methyl acetamide (**28**)*

To a stirred solution of **27** (37.1 mg, 0.0921 mmol, 1.0 equiv) in dry toluene (1 mL) at room temperature was added Lawesson's reagent (18.6 mg, 0.0460 mmol, 0.51 equiv). The resulting yellow suspension was stirred at room temperature for 21 h. The reaction mixture was then concentrated in vacuo. Purification by silica gel flash chromatography (33% ethyl acetate in hexanes) provided **28** (33 mg, 86%) as a colorless oil. R_f=0.47 (33% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (dd, 1H, *J*=6.5, 2.5 Hz, $CH_2CHOTBS$), 4.21 (ddt, 1H, *J*=8.7, 6.6, 3.4 Hz, CH_2CHN), 3.95 (d, 1H, *J*=14.5 Hz, $TMSCH_2N$), 3.67 (s, 3H, $NOCH_3$), 3.20 (s, 3H, NCH_3), 3.02 (dd, 1H, *J*=16.4, 3.8 Hz, $CH_2C(O)N(CH_3)OCH_3$), 2.85, (d, 1H, *J*=14.5 Hz, $TMSCH_2N$), 2.83 (dd, 1H, *J*=16.4, 8.7 Hz, $CH_2C(O)N(CH_3)OCH_3$), 2.47 (dt, 1H, *J*=13.5, 7.1 Hz, $CH_2CHOTBS$), 1.78 (dt, 1H, *J*=13.3, 2.8 Hz, $CH_2CHOTBS$), 0.89 (s, 9H, TBS *tert*-butyl), 0.20 (s, 3H, TBS methyl), 0.19 (s, 3H, TBS methyl), 0.14 (s, 9H, TMS); FTIR (neat film, NaCl) 2953, 1666, 1472, 1416, 1388, 1360, 1250, 1153, 1128, 1082, 1005, 908, 884, 842, 779 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{18}H_{39}N_2O_3S_1Si_2$ (MH^+) 419.2220, found 419.2219.

*4.13. 2-[4-(tert-Butyl-dimethyl-silanyloxy)-5-(2-oxo-butylidene)-1-trimethylsilanyl-methyl-pyrrolidin-2-yl]-N-methoxy-N-methyl acetamide (**29**)*

To a stirred solution of **28** (24.7 mg, 0.0589 mmol, 1.0 equiv) in dichloromethane (1 mL) was added 1-bromo-2-butanone (7.0 μL, 0.065 mmol, 1.1 equiv). The colorless solution was then concentrated in vacuo. The colorless oil was heated neat at 60 °C for 10 min. The resulting white solid was dissolved in dichloromethane (1 mL), and triphenylphosphine (17.0 mg, 0.0648 mmol, 1.1 equiv) and triethylamine (9.0 μL, 0.065 mmol, 1.1 equiv) were added. The resulting yellow solution was then stirred for 21 h at room temperature and concentrated. Purification by silica gel flash chromatography (33% ethyl acetate in hexanes) provided **29** (14.1 mg, 52%, (*E*)-isomer only) as a colorless oil. R_f=0.31 (33% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (d, 1H, *J*=5.5 Hz, $CH_2CHOTBS$), 4.78 (s, 1H, vinyl H), 3.92 (m, 1H, CH_2CHN), 3.65 (s, 3H, $NOCH_3$), 3.19 (s, 3H, NCH_3), 2.94 (m, 2H, $CH_2C(O)N(CH_3)OCH_3$), 2.84 (d, 1H, *J*=15.6 Hz, $TMSCH_2N$), 2.68 (d, 1H, *J*=15.6 Hz, $TMSCH_2N$), 2.27 (q, 2H, *J*=7.3 Hz, CH_2CH_3), 2.13 (ddd, 1H, *J*=13.2, 8.8, 5.1 Hz, $CH_2CHOTBS$), 1.83 (d, 1H, *J*=13.2 Hz, $CH_2CHOTBS$), 1.10 (t, 3H, *J*=7.4 Hz, CH_2CH_3), 0.83 (s, 9H, TBS *tert*-butyl), 0.26 (s, 3H, TBS methyl), 0.12 (s, 9H, TMS), 0.10 (s, 3H, TBS methyl); FTIR (neat film, NaCl) 2954, 1664, 1558, 1462, 1412, 1386, 1305, 1250, 1117, 853, 779 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{22}H_{45}N_2O_4Si_2$ (MH^+) 457.2918, found 457.2918.

*4.14. 1-[4-(tert-Butyl-dimethyl-silanyloxy)-5-(2-oxo-butylidene)-1-trimethylsilanyl-methyl-pyrrolidin-2-yl]-4-ethylsulfanyl-but-3-en-2-one (**30**)*

To a stirred solution of **29** (15.2 mg, 0.0333 mmol, 1.0 equiv) in dry tetrahydrofuran (1 mL) at room temperature was added ethynylmagnesium chloride (0.5 M solution in tetrahydrofuran, 400 μL, 0.200 mmol, 6.0 equiv) and the resulting yellow solution was stirred for 1 h. The reaction mixture was then filtered through a short pad of silica gel (ethyl acetate) and the filtrate concentrated. The resulting bright yellow oil was then dissolved in dichloromethane (1 mL). Ethane thiol (3.0 μL, 0.036 mmol, 1.1 equiv) and triethylamine (10 μL, 0.073 mmol, 2.2 equiv) were then added at room temperature. The resulting solution was stirred at room temperature for 8 h

and then concentrated in vacuo. Purification by silica gel flash chromatography (25% ethyl acetate in hexanes) provided **30** (9.2 mg, 57%, (*E*)-isomer only) as a pale yellow oil. R_f=0.52 (33% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, 1H, J=16.0 Hz, CH_3CH_2SCH=CH−C=O), 6.11 (d, 1H, J=16.0 Hz, CH_3CH_2SCH=CH−C=O), 5.81 (d, 1H, J=5.4 Hz, CH_2CHOTBS), 4.79 (s, 1H, vinyl H), 3.96 (br m, 1H, CH_2CHN), 3.10 (dd, 1H, J=16.9, 7.8 Hz, CH_2C(O)CH=CHSCH$_2$CH$_3$), 2.98 (dd, 1H, J=16.9, 4.6 Hz, CH_2C(O)CH=CHSCH$_2$CH$_3$), 2.84 (d, 1H, J=15.6 Hz, TMSCH_2N), 2.80 (q, 2H, J=7.3 Hz, SCH_2CH$_3$), 2.57 (d, 1H, J=15.6 Hz, TMSCH_2N), 2.29 (q, 2H, J=7.4 Hz, CH_2CH$_3$), 2.04 (m, 1H, CH_2CHOTBS), 1.69 (m, 1H, CH_2CHOTBS), 1.38 (t, 3H, J=7.3 Hz, SCH$_2$CH_3), 1.14 (t, 3H, J=7.4 Hz, CH$_2$CH_3), 0.86 (s, 9H, TBS *tert*-butyl), 0.26 (s, 3H, TBS methyl), 0.12 (s, 9H, TMS), 0.078 (s, 3H, TBS methyl); FTIR (neat film, NaCl) 2928, 1653, 1557, 1458, 1366, 1250, 1207, 1082, 839 cm^{-1}; HRMS (FAB) *m/z*: calcd for $C_{24}H_{46}N_1O_3S_1Si_2$ (MH^+) 484.2737, found 484.2735.

*4.15. Acetic acid 2,2-dimethyl-6-oxo-5-trimethylsilanylmethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrol-4-yl ester (**40**)*

To a solution of lactone **39** (4.9 g, 31 mmol, 1.0 equiv) in tetrahydrofuran (30 mL) were added triethylamine (5.6 mL, 40 mmol, 1.3 equiv) and *C*-trimethylsilanyl-methylammonium hydrochloride (5.6 g, 40 mmol, 1.3 equiv). The flask was sealed under argon and heated to 70 °C for 18 h. After cooling to room temperature, the resulting orange suspension was transferred to a separatory funnel containing deionized water (300 mL) and extracted with dichloromethane (3×300 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo providing 5-hydroxymethyl-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid trimethylsilanylmethyl-amide (7.8 g, 97%) as a brown solid, which was used without further purification. R_f=0.16 (33% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (br s, 1H, CONH), 4.62 (d, 1H, J=7.6 Hz, COCHCHCH$_2$), 4.54 (ddd, 1H, J=8.6, 7.7, 4.6 Hz, COCHCHCH$_2$), 3.81 (dd, 1H, J=11.8, 4.6 Hz, COCHCHCH$_2$), 3.55 (dd, 1H, J=11.8, 8.7 Hz, COCHCHCH$_2$), 2.96 (dd, 1H, J=15.4, 7.0 Hz, NCH_2), 2.66 (dd, 1H, J=15.0, 5.0 Hz, NCH_2), 1.54 (s, 3H, C(CH_3)$_2$), 1.40 (s, 3H, C(CH_3)$_2$), 0.10 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 110.1, 77.7, 77.4, 61.9, 29.4, 27.2, 24.6, −2.6; FTIR (neat film, NaCl) 3272, 2987, 2956, 1644 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{11}H_{24}NO_4Si$ (MH^+) 262.1474, observed 262.1471. To a solution of 5-hydroxymethyl-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid trimethylsilanylmethyl-amide (4.0 g, 15.3 mmol, 1.0 equiv) in dimethylsulfoxide (30 mL) was added triethylamine (15 mL, 107 mmol, 7.0 equiv). Sulfur trioxide–pyridine complex (9.7 g, 61 mmol, 4.0 equiv) was added via cannula in a solution in dimethylsulfoxide (30 mL). After stirring at room temperature for 6 h, the resulting clear orange solution was transferred to a separatory funnel containing ice water (500 mL) and extracted with dichloromethane (3×700 mL). The combined organic extracts were concentrated in vacuo to a volume of 500 mL and washed sequentially with a 1:1 solution of 1 N aqueous hydrochloric acid and brine (1×100 mL) and a 4:1 solution of brine and saturated aqueous sodium bicarbonate (1×100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo, affording the desired hemiaminal, which was carried forward without further purification. Hemiaminal was dissolved in pyridine (30 mL) and acetic anhydride (7.3 mL, 77 mmol, 5.0 equiv) was added to the solution. After stirring for 42 h at room temperature, the resulting clear brown solution was transferred to a separatory funnel containing ethyl acetate (500 mL). The organic layer was washed sequentially with 0.5 M aqueous hydrochloric acid (2×200 mL) and a 9:1 solution of brine and saturated aqueous sodium bicarbonate (1×200 mL). The organic layer was dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by silica gel column chromatography (33% ethyl acetate in hexanes) affording aminal **40** (3.2 g, 69%) as a pale yellow oil. R_f=0.51 (50% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (s, 1H, NCHCHCH), 4.74 (d, 1H, J=6.0 Hz, NCHCHCH), 4.49 (d, 1H, J=5.6 Hz, NCHCHCH), 3.12 (d, 1H, J=15.3, NCH_2), 2.46 (dd, 1H, J=15.3, 0.7 Hz, NCH_2), 2.11 (s, 3H, COCH_3), 1.44 (s, 3H, C(CH_3)$_2$), 1.36 (s, 3H, C(CH_3)$_2$), 0.11 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.1, 153.3, 113.8, 86.9, 76.2, 32.5, 27.0, 25.7, 21.1, 8.7, −1.6; FTIR (neat film, NaCl) 2954, 1746, 1719 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{13}H_{23}NNaO_5Si$ (MNa^+) 324.1243, observed 324.1247.

*4.16. (2,2-Dimethyl-6-oxo-5-trimethylsilanylmethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrol-4-yl)-acetic acid (**42**)*

To a solution of aminal **40** (154 mg, 0.511 mmol, 1.0 equiv) in dichloromethane (5 mL) was added silyl ketene acetal **41** (207 mg, 1.02 mmol, 2.0 equiv) followed by trimethylsilyl trifluoromethanesulfonate (18 μL, 0.102 mmol, 0.20 equiv). After stirring at room temperature for 26 h, the reaction was quenched with saturated aqueous sodium bicarbonate (1 mL) and the mixture transferred to a separatory funnel containing deionized water (50 mL). Following extraction with dichloromethane (3×100 mL), the combined organic extracts were dried over sodium sulfate, filtered, concentrated in vacuo, and purified by silica gel column chromatography (20% ethyl acetate in dichloromethane) affording (2,2-dimethyl-6-oxo-5-trimethylsilanylmethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)-acetic acid ethyl ester (121 mg, 72%) as a colorless oil. R_f=0.37 (50% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (d, 1H, J=6.0 Hz, COCHCHCHCH$_2$), 4.60 (d, 1H, J=5.9 Hz, COCHCHCHCH$_2$), 4.14 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 3.86 (dd, 1H, J=7.5, 3.2 Hz, COCHCHCHCH$_2$), 3.33 (d, 1H, J=15.4 Hz, NCH_2), 2.70 (dd, 1H, J=16.2, 3.3 Hz, COCHCHCHCH$_2$), 2.55 (dd, 1H, J=16.2, 7.6 Hz, COCHCHCHCH$_2$), 2.21 (dd, 1H, J=15.4, 0.7 Hz), 1.45 (s, 3H, C(CH_3)$_2$), 1.36 (s, 3H, C(CH_3)$_2$), 1.25 (t, 3H, OCH$_2$CH_3), 0.12 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 170.0, 112.4, 77.4, 77.3, 61.4, 60.7, 35.1, 32.0, 27.1, 25.5, 14.3, −1.4; FTIR (neat film, NaCl) 2986, 1734, 1696 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{15}H_{28}NO_5Si$ (MH^+) 330.1737,

observed 330.1724. To a solution of (2,2-dimethyl-6-oxo-5-trimethylsilanylmethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)-acetic acid ethyl ester (2.38 g, 7.22 mmol, 1.0 equiv) in THF (130 mL) was added 1.0 M aqueous lithium hydroxide (21.7 mL, 21.7 mmol, 3.0 equiv). After stirring at room temperature for 3 h, the resulting pale yellow suspension was transferred into a separatory funnel containing 500 mL 0.5 M aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (3×600 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated, providing **42** (2.09 g, 96%) as a pale yellow foam. R_f=0.20 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85 (d, 1H, J=5.8 Hz, COC*H*CH), 4.65 (d, 1H, J=5.9 Hz, COCHC*H*), 3.84 (dd, 1H, J=6.6, 3.3 Hz, NC*H*CH_2), 3.74 (app t, 1H, J=6.5 Hz, CO_2H), 3.31 (d, 1H, J=15.3 Hz, NCH_2), 2.71 (dd, 1H, J=16.5, 3.3 Hz, NCHCH_2), 2.64 (dd, 1H, J=16.5, 6.6 Hz, NCHCH_2), 2.24 (d, 1H, J=15.3 Hz, NCH_2), 1.42 (s, 3H, C(CH_3)$_2$), 1.34 (s, 3H, C(CH_3)$_2$), 0.10 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 171.8, 112.3, 77.6, 68.1, 61.2, 34.4, 32.2, 27.0, 25.5, −1.4; FTIR (neat film, NaCl) 3448, 2989, 1729, 1659 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{23}NO_5SSi$ (M^+) 302.1424, observed 302.1425.

4.17. 2-(2,2-Dimethyl-6-thioxo-5-trimethylsilanylmethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrol-4-yl)-N-methoxy-N-methyl-acetamide (*43*)

A solution of lactam **42** (1.68 g, 5.57 mmol, 1.0 equiv) in toluene (56 mL) was charged with Lawesson's reagent (1.24 g, 3.07 mmol, 0.55 equiv), sealed, and heated to 65 °C for 16 h. The resulting pale yellow solution was concentrated in vacuo and purified directly by silica gel column chromatography (dichloromethane followed by 3% acetic acid in ethyl acetate) to afford (2,2-dimethyl-6-thioxo-5-trimethylsilanylmethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)-acetic acid (1.68 g, 95%) as a pale yellow oil. R_f=0.44 (3% acetic acid in ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96 (dd, 1H, J=5.4, 1.3 Hz, NCHCHC*H*), 4.58 (d, 1H, J=5.4 Hz, NCHC*H*CH), 4.23 (dd, 1H, J=8.1, 3.8 Hz, NC*H*CHCH), 4.20 (d, 1H, J=14.8 Hz, NCH_2TMS), 3.08 (dd, 1H, J=16.8, 3.8 Hz, HOC═OCH_2), 2.88 (dd, 1H, J=16.8, 8.1 Hz, HOC═OCH_2), 2.56 (dd, 1H, J=14.8, 1.4 Hz, NCH_2TMS), 2.11 (s, 1H, *H*OC═OCH_2), 1.46 (s, 3H, C(CH_3)$_2$), 1.37 (s, 3H, C(CH_3)$_2$), 0.18 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.0, 193.6, 113.0, 86.4, 78.0, 67.4, 44.8, 38.3, 27.2, 25.8, −0.7; FTIR (neat film, NaCl) 2954, 1693, 1491 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{24}NO_4SSi$ (MH^+) 318.1195, observed 318.1180. To a solution of (2,2-dimethyl-6-thioxo-5-trimethylsilanylmethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl)-acetic acid (1.75 g, 5.51 mmol, 1.0 equiv) in dichloromethane (28 mL) was added sequentially *N*,*O*-dimethylhydroxylamine hydrochloride (1.07 g, 11.0 mmol, 2.0 equiv), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.11 g, 11.0 mmol, 2.0 equiv), and triethylamine (3.85 mL, 27.6 mmol, 5.0 equiv). After stirring 15 h at room temperature, the resulting brown suspension was transferred to a separatory funnel containing 300 mL saturated aqueous ammonium chloride and extracted with dichloromethane (3×500 mL). The combined organic fractions were dried over sodium sulfate, filtered, concentrated in vacuo, and filtered through a plug of silica gel with ethyl acetate. Concentration afforded **43** (1.24 g, 62%) as a pale yellow oil. R_f=0.66 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96 (dd, 1H, J=5.5, 1.1 Hz, NCHCHC*H*), 4.59 (d, 1H, J=5.4 Hz, NCHC*H*CH), 4.28 (dd, 1H, J=8.9, 3.7 Hz, NC*H*CHCH), 4.12 (d, 1H, J=14.7 Hz, NCH_2TMS), 3.68 (s, 3H, NOCH_3), 3.17 (s, 3H, NCH_3), 2.84 (dd, 1H, J=16.7, 3.5 Hz, (MeO)NMeC═OCH_2), 2.63 (dd, 1H, J=16.5, 8.9 Hz, (MeO)NMeC═OCH_2), 2.59 (dd, 1H, J=14.6, 1.2 Hz, NCH_2TMS), 1.44 (s, 3H, C(CH_3)$_2$), 1.34 (s, 3H, C(CH_3)$_2$), 0.15 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.6, 169.8, 112.6, 86.5, 78.5, 67.6, 61.7, 38.2, 32.3, 27.3, 25.7, 14.6, −0.7; FTIR (neat film, NaCl) 2953, 1655, 1491 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{15}H_{28}N_2O_4SSi$ (MH^+) 361.1617, observed 361.1620.

4.18. 1-[2,2-Dimethyl-6-(2-oxo-butylidene)-5-trimethylsilanylmethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrol-4-yl]-4-ethylsulfanyl-but-3-en-2-one (*44*)

To a solution of **43** (607 mg, 1.68 mmol, 1.0 equiv) in acetonitrile (34 mL) was added 1-bromo-2-butanone (180 μL, 1.77 mmol, 1.05 equiv) at room temperature. After 22 h, triphenylphosphine (485 mg, 1.85 mmol, 1.1 equiv) was added followed by triethylamine (260 μL, 1.85 mmol, 1.1 equiv). The resulting pale orange solution was stirred for 90 min at room temperature before being concentrated in vacuo to 5 mL. The crude reaction solution was purified directly by silica gel column chromatography (50% hexane in ethyl acetate ramped to 100% ethyl acetate) affording 2-[2,2-dimethyl-6-(2-oxo-butylidene)-5-trimethylsilanylmethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl]-*N*-methoxy-*N*-methyl-acetamide (545 mg, 81%) as a pale yellow oil. R_f=0.09 (ethyl acetate); ^{1}H NMR (500 MHz, C_6D_6) δ 6.22 (d, 1H, J=6.0 Hz, NCHCHC*H*), 4.96 (s, 1H, vinyl H), 4.39 (d, 1H, J=6.0 Hz, NCHC*H*CH), 4.17 (dd, 1H, J=8.4, 4.2 Hz, NC*H*CHCH), 2.85 (s, 3H, NOCH_3), 2.71 (s, 3H, NCH_3), 2.55 (d, 1H, J=15.3 Hz, NCH_2TMS), 2.41 (q, 1H, J=7.5 Hz, CH_3CH_2C═O), 2.39 (q, 1H, J=7.6 Hz, CH_3CH_2C═O), 2.34 (m, 1H, (MeO)NMeC═OCH_2), 2.23 (d, 1H, J=15.5 Hz, NCH_2TMS), 2.10 (dd, 1H, J=16.1, 8.3 Hz, (MeO)NMeC═OCH_2), 1.39 (s, 3H, C(CH_3)$_2$), 1.23 (s, 3H, C(CH_3)$_2$), 1.21 (t, 3H, J=7.3 Hz, CH_3CH_2C═O), 0.04 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (126 MHz, C_6D_6) δ 194.7, 170.6, 160.2, 110.9, 91.3, 81.0, 80.2, 66.0, 60.6, 36.6, 35.1, 33.1, 31.6, 27.2, 25.3, 9.7, −1.4; FTIR (neat film, NaCl) 2937, 1656, 1556 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{35}N_2O_5Si$ (MH^+) 399.2315, observed 399.2327. To a solution of 2-[2,2-dimethyl-6-(2-oxo-butylidene)-5-trimethylsilanylmethyl-tetrahydro-[1,3]dioxolo-[4,5-*c*]pyrrol-4-yl]-*N*-methoxy-*N*-methyl-acetamide (545 mg, 1.37 mmol, 1.0 equiv) in tetrahydrofuran (23 mL) at room temperature was added ethynylmagnesium bromide (0.5 M solution in tetrahydrofuran, 6.6 mL, 3.28 mmol, 2.4 equiv). After stirring for 2 h, the reaction solution was filtered through a plug of silica gel with ethyl acetate. Concentration of the solution via rotary evaporation to about 10 mL volume was followed by dilution with dichloromethane to about 30 mL total volume.

After repeating this procedure four times, ethane thiol (111 μL, 1.50 mmol, 1.1 equiv) was added at room temperature followed by triethylamine (360 μL, 2.60 mmol, 1.9 equiv). The reaction solution was stirred for 19 h at room temperature, and then poured into a separatory funnel containing 150 mL dichloromethane and partitioned with 100 mL deionized water. The aqueous layer was extracted with dichloromethane (2×150 mL) and the combined organic fractions were dried over sodium sulfate, filtered, and concentrated in vacuo affording **44** (337 mg, 58%) as a pale yellow oil. R_f=0.24 (diethyl ether); ^{1}H NMR (500 MHz, C_6D_6) δ 7.50 (d, 1H, J=15.3 Hz, CH_3CH_2SCH=CHC=OCH_2), 6.16 (d, 1H, J=5.8 Hz, NCHCHC*H*), 5.86 (d, 1H, J=15.3 Hz, CH_3CH_2SCH=C*H*C=OCH_2), 4.95 (s, 1H, CH_3CH_2C=OC*H*=C), 4.22 (d, 1H, J=6.0 Hz, NCHC*H*CH), 4.17 (dd, 1H, J=8.2, 4.2 Hz, NC*H*CHCH), 2.50 (d, 1H, J=15.8 Hz, NCH_2TMS), 2.41 (q, 2H, J=7.9 Hz, CH_3CH_2SCH=CHC=OCH_2), 2.40 (q, 2H, J=7.8 Hz, CH_3CH_2SCH=CHC=OCH_2), 2.19 (dd, 1H, J=17.1, 4.1 Hz, CH_3CH_2SCH=CHC=OCH_2), 2.15 (q, 2H, J=7.2 Hz, CH_3CH_2C=OCH=C), 2.14 (d, 1H, J=15.4 Hz, NCH_2TMS), 1.92 (dd, 1H, J=17.1, 8.4 Hz, CH_3CH_2SCH=CHC=OCH_2), 1.39 (s, 3H, C(CH_3)$_2$), 1.22 (s, 3H, C(CH_3)$_2$), 1.21 (t, 3H, J=7.5 Hz, CH_2CH_3), 0.82 (t, 3H, J=7.5 Hz, CH_2CH_3), 0.04 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (126 MHz, C_6D_6) δ 194.8, 192.2, 160.3, 147.3, 122.5, 111.0, 91.0, 81.0, 80.2, 65.5, 40.8, 36.6, 35.1, 27.2, 26.0, 25.3, 13.5, 9.7, −1.4; FTIR (neat film, NaCl) 2963, 1648, 1553 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{21}H_{35}NO_4SSi$ (MH^+) 426.2134, observed 426.2143.

4.19. Bridged pyrrolizidine **45**

To a solution of **44** (1.32 g, 3.10 mmol, 1.0 equiv) in chloroform (220 mL) at −45 °C was added trifluoromethanesulfonic anhydride (570 μL, 3.41 mmol, 1.1 equiv). The resulting colorless solution was stirred at −45 °C for 15 min, warmed to 0 °C, and stirred for 20 min and then recooled to −45 °C. Tetrabutylammonium triphenyldifluorosilicate (1.84 g, 3.41 mmol, 1.1 equiv) was added and the solution was allowed to warm to room temperature slowly over 15 h. The resulting clear, purple solution was concentrated in vacuo and purified by silica gel column chromatography (1% methanol in dichloromethane, ramped to 2% methanol in dichloromethane), providing **45** (1.07 g, 71%) as a colorless oil. R_f=0.30 (diethyl ether); ^{1}H NMR (500 MHz, C_6D_6) δ 5.21 (s, 1H, vinyl *H*), 4.99 (d, 1H, J=3.4 Hz, $COCH_2CHCHC$*H*), 4.06 (d, 1H, J=5.8 Hz, $COCH_2CHC$*H*CH), 3.49 (s, 1H, COC*H*$CHCH_2$), 3.24 (d, 1H, J=5.5 Hz, $COCH_2C$*H*CHCH), 3.02 (d, 2H, J=6.1 Hz, $COCHCHC$*H*$_2$), 2.73 (t, 1H, J=6.3 Hz, COCHC*H*CH_2), 2.32 (quartet, 2H, J=7.4 Hz, C(OTf)CH_2CH_3), 2.25 (quartet, 2H, J=7.4 Hz, SCH_2CH_3), 1.79 (dd, 1H, J=16.0, 6.3 Hz, $COCH_{2(ax)}$CHCHCH), 1.60 (d, 1H, J=16.0 Hz, $COCH_{2(eq)}$-CHCHCH), 1.54 (s, 3H, C(CH_3)$_2$), 1.19 (s, 3H, C(CH_3)$_2$), 1.03 (t, 3H, J=7.4 Hz, SCH_2CH_3), 0.98 (t, 3H, J=7.4 Hz, C(OTf)CH_2CH_3); ^{13}C NMR (126 MHz, C_6D_6) δ 203.9, 150.4, 120.0, 118.9, 112.0, 83.4, 80.2, 79.3, 66.9, 64.3, 56.1, 48.6, 39.8, 27.6, 26.6, 26.3, 25.3, 14.6, 10.7; FTIR (neat film, NaCl) 2965, 1712, 1560, 1430, 1260 cm^{-1}; $[\alpha]_D^{24}$ −213.0 (*c* 0.034, $CHCl_3$); HRMS (ESI) *m/z*: calcd for $C_{19}H_{27}F_3NO_6S_2$ (MH^+) 486.1232, observed 486.1234.

4.20. Bridged pyrrolizidine **46**

To a solution of **45** (350 mg, 0.721 mmol) in methanol (300 mL) was added 10% palladium on carbon (1.00 g) and the resulting black suspension was charged with hydrogen gas via balloon and stirred under an atmosphere of hydrogen for 18 h. Filtration through Celite, concentration in vacuo, and purification of the residue by silica gel column chromatography (50% ethyl acetate in hexanes) provided **46** (214 mg, 89%) as a colorless oil. R_f=0.46 (ethyl acetate); ^{1}H NMR (500 MHz, C_6D_6) δ 4.37 (d, 1H, J=6.0 Hz, $COCH_2CHCHCH$), 4.04 (d, 1H, J=6.0 Hz, $COCH_2CHCHCH$), 3.27 (d, 1H, J=6.0 Hz, $COCH_2CHCHCH$), 3.13 (dd, 1H, J=14.0, 5.1 Hz, $COCHCHCH_2$), 3.03 (s, 1H, COC*H*$CHCH_2$), 2.97 (dd, 1H, J=14.0, 8.3 Hz, $COCHCHCH_2$), 2.63 (dd, 1H, J=8.3, 5.1 Hz, COCHC*H*CH_2), 2.12 (q, 2H, J=7.4 Hz, SCH_2CH_3), 2.05 (m, 2H, $CH_2(CH_2)_2CH_3$), 1.81 (dd, 1H, J=15.8, 6.2 Hz, $COCH_2CHCHCH$), 1.56 (d, 1H, J=15.8 Hz, $COCH_2CHCHCH$), 1.50 (s, 3H, C(CH_3)$_2$), 1.49−1.33 (m, 4H, $CH_2(CH_2)_2CH_3$), 1.09 (s, 3H, C(CH_3)$_2$), 0.93 (t, 3H, J=7.4 Hz, CH_2CH_3), 0.90 (t, 3H, J=7.2 Hz, CH_2CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.7, 111.5, 82.7, 81.0, 79.5, 79.2, 65.0, 64.7, 56.8, 40.5, 29.9, 28.3, 26.3, 26.0, 24.9, 23.1, 15.1, 14.0; FTIR (neat film, NaCl) 2958, 2927, 1712, 1459, 1379 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{18}H_{30}NO_3S$ (MH^+) 339.1868, observed 339.1868.

4.21. Bridged pyrrolizidine **47**

A solution of **46** (13 mg, 0.038 mmol, 1.0 equiv) in tetrahydrofuran (600 μL) was cooled to 0 °C and charged with a solution of 0.2 M LDA in tetrahydrofuran (260 μL, 1.2 equiv). After stirring for 1 h, ethyl iodoacetate (5.4 μL, 0.046 mmol, 1.2 equiv) was added and the solution was stirred for a further 30 min at 0 °C and then quenched with saturated aqueous sodium bicarbonate. The product was extracted from deionized water (5 mL) with ethyl acetate (3×10 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (29% ethyl acetate in hexanes, ramped to 50% ethyl acetate in hexanes), providing **47** (9.5 mg) as a 1:1 mixture of C-12 epimers. This mixture was dissolved in toluene (500 μL) and charged with DBU (13.3 μL, 0.089 mmol, 4.0 equiv), and the resulting solution was stirred at 80 °C for 16 h. Elution of the solution through a plug of silica gel with ethyl acetate provided, upon concentration, **46** (9.5 mg, 58% over two steps) as a colorless oil. R_f=0.32 (50% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 4.32 (d, 1H, J=6.1 Hz, $COCHCHCHCH$), 4.09 (d, 1H, J=6.1 Hz, $COCHCHCHCH$), 3.95 (q, 1H, J=7.2 Hz, OCH_2CH_3), 3.93 (q, 1H, J=7.2 Hz, OCH_2CH_3), 3.39 (d, 1H, J=5.7 Hz, COC*H*$CHCH_2$), 3.20 (d, 2H, J=6.6 Hz, CH_2CO_2Et), 3.15 (s, 1H, COCHC*H*CHCH), 3.09 (ddd, 1H, J=8.8, 5.5, 4.1 Hz, COCHC*H*CH_2), 3.03 (t, 1H, J=6.6 Hz, COC*H*CHCHCH),

2.74 (dd, 1H, J=16.9, 8.8 Hz, COCHCHCH_2), 2.16–2.02 (m, 4H, SCH_2CH$_3$, CH_2(CH$_2$)$_2$CH$_3$), 1.70 (dd, 1H, J=16.9, 4.1 Hz, COCHCHCH_2), 1.52 (t, 3H, C(CH_3)$_2$), 1.51–1.34 (m, 4H, CH$_2$(CH_2)$_2$CH$_3$), 1.11 (s, 3H, C(CH_3)$_2$), 0.96 (t, 3H, J=7.1 Hz, CH$_2$CH_3), 0.93 (t, 3H, J=7.3 Hz, CH$_2$CH_3), 0.91 (t, 3H, J=7.4 Hz, CH$_2$CH_3); ^{13}C NMR (126 MHz, CDCl$_3$) δ 207.1, 171.8, 111.4, 81.3, 79.2, 79.0, 69.6, 63.7, 61.2, 57.0, 49.3, 44.2, 30.0, 29.8, 28.5, 26.5, 26.1, 24.9, 23.1, 15.2, 14.3, 14.1; FTIR (neat film, NaCl) 2960, 2927, 1732, 1708, 1560, 1412 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{22}H_{36}NO_5S$ (MH$^+$) 425.2236, observed 425.2233.

4.22. Bridged pyrrolizidine **48**

A solution of **47** (2.6 mg, 0.0061 mmol) was charged with 2.5 M aqueous hydrochloric acid (750 μL), sealed under argon, and heated to 60 °C for 3.5 h. Concentration in vacuo provided **48** (2.1 mg, 96%) as a colorless film. ^{1}H NMR (500 MHz, CD$_3$OD) δ 4.54 (dd, 1H, J=14.1, 8.6 Hz, COCHCHCH_2), 4.39 (d, 1H, J=5.3 Hz, COCHCHCHCH), 4.23 (d, 1H, J=6.0 Hz, COCHCHCHCH), 4.05 (d, 1H, J=5.3 Hz, COCHCHCHCH), 3.78 (dd, 1H, J=8.6, 5.2 Hz, COCHCHCH$_2$), 3.68 (m, 2H, COCHCHCH_2, COCHCHCHCH), 2.88 (dd, 1H, J=17.4, 7.4 Hz, CH_2CO$_2$H), 2.78 (q, 2H, J=7.4 Hz, SCH_2CH$_3$), 2.43 (dd, 1H, J=17.4, 5.6 Hz, CH_2CO$_2$H), 2.08 (m, 2H, CH_2(CH$_2$)$_2$CH$_3$), 1.47 (m, 4H, CH$_2$(CH_2)$_2$CH$_3$), 1.33 (t, 3H, J=7.4 Hz, SCH$_2$CH_3), 1.01 (t, 3H, J=7.2 Hz, CH$_2$(CH$_2$)$_2$CH_3); FTIR (neat film, NaCl) 3411, 3137, 2960, 2925, 2868, 1727, 1711, 1158 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{17}H_{28}NO_5S$ (MH$^+$) 358.1688, observed 358.1690.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.008.

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25. The *trans*-configuration was inferred from comparison of coupling constant values to that of **27** (vide infra), as well as the lack of NOE signal between the C9a and C2 methine protons. No positive diagnostic NOE signals were observed.
26. Cycloaddition conditions involving chloroform, dichloromethane, acetonitrile, and benzene as solvent, TBAT and CsF as fluoride sources and desilylation temperatures ranging from −78 to 23 °C failed to prevent C2 epimerization.