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Enantioselective synthesis of (+)-anatoxin-a via enyne metathesis

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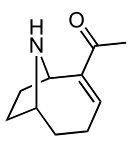
Dedicated to Professor Robert H. Grubbs in recognition of his many contributions to organic chemistry and his receipt of the Tetrahedron Prize

Abstract—A concise synthesis of the potent *n*AChR agonist (+)-anatoxin-a (**1**) has been completed by a series of nine chemical operations and in 27% overall yield from commercially available D-methyl pyroglutamate (**12**). The strategy featured the application of a new protocol for the diastereoselective synthesis of *cis*-2,5-disubstituted pyrrolidines bearing unsaturated side chains and an intramolecular enyne metathesis to provide the bridged bicyclic framework of **1**. Thus, D-methyl pyroglutamate (**12**) was converted in five steps to **32**, which underwent facile enyne metathesis to deliver the bicyclic diene **33**. Selective oxidative cleavage of the less substituted carbon–carbon double bond in **33** followed by deprotection furnished (+)-anatoxin-a (**1**).

1. Introduction

The design and development of general and efficient strategies for alkaloid synthesis has long been a central objective in our laboratories. In that context, we became interested in applying ring-closing metathesis (RCM) to forming nitrogen heterocyclic subunits that are common to different polycyclic alkaloids since the seminal discovery by Grubbs and Fu in 1992[1] that RCM could be applied to the formation of heterocycles.[2,3] We subsequently established the efficacy of RCM for the facile construction of not only simple fused nitrogen heterocycles,[4] but of more complex targets such as dihydrocorynantheol[5] and the anticancer alkaloids manzamine A[6] and FR900482.[7] More recently we disclosed a general entry to azabicyclo[*m.n.*1]alkenes (*m*=3–5, *n*=2, 3) by the ring-closing metathesis of *cis*-2,6-dialkenyl-*N*-acyl piperidines.[8] In a related development, we exploited the RCM of a dialkenyl pyrrolidine as a key step in a concise synthesis of the anticancer alkaloid peduncularine.[9]

It was a logical extension of the aforementioned studies to determine the feasibility of a RCM approach to the unusual azabicyclo[4.2.1]nonene skeleton found in the potent neurotoxic alkaloid anatoxin-a (**1**). (+)-Anatoxin-a (**1**) was isolated from the toxic blooms of the blue–green freshwater algae *Anabaena flos-aquae* (Lyngb.) de Bréb and is one of the most potent nicotinic acetylcholine receptor (*n*AChR) agonists known.[10] Also referred to as 'very fast death factor' (VFDF), **1** has been shown to resist enzymatic degradation by acetylcholine esterase, resulting in respiratory paralysis and eventual death.[11] Despite its toxicity, **1** has emerged as a valuable chemical probe for elucidating the mechanism of acetylcholine-mediated neurotransmission and the disease states associated with abnormalities in this important signaling pathway. Consequent to its potent pharmacological profile and unique 9-azabicylo[4.2.1]-nonane skeleton, **1** has remained an attractive synthetic target since its isolation in 1977.[12] A variety of nonlethal analogs that contain the 9-azabicylo[4.2.1]nonane skeleton have recently been identified as potential therapeutic targets for treating neurological disorders such as Alzheimer's and Parkinson's diseases, schizophrenia and depression.[13] We now report the details of a highly efficient synthesis of **1** employing a strategy that features a new method for the diastereoselective synthesis of *cis*-2,5-disubstituted pyrrolidines and an intramolecular enyne metathesis.[14–16]



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2. Results and discussion

Although we had prepared the five-membered ring of azabicyclo[3.2.1]octenes by the RCM of *cis*-2,6-divinyl piperidines,[8] the stereoselective synthesis of a suitable

Keywords: Enantioselective synthesis; Ring closing metathesis; Diastereoselective reduction; Pyrrolidine; Iminium ion.
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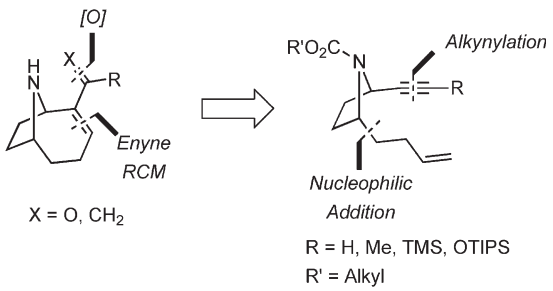
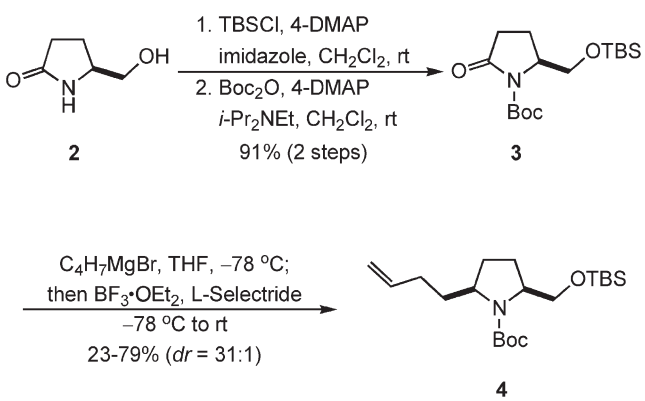
cis-2,7-divinylazepane that would lead to **1** seemed rather daunting. Hence, we were inspired to develop a route to **1** that featured the formation of the seven-membered ring of the bridged bicyclic ring system of **1** by the RCM of an appropriate enyne (Scheme 1). Oxidative cleavage of the pendant olefinic bond would then unveil the α,β-unsaturated ketone moiety of **1**. In order to implement this attractive strategy, it would be necessary to prepare a *cis*-2,5-disubstituted-*N*-acyl pyrrolidine having unsaturated side chains as the prelude to the pivotal RCM.



Scheme 1.

Examination of the literature revealed that the available methods for the efficient and diastereoselective preparation of *cis*-2,5-disubstituted pyrrolidines incorporating unsaturated moieties was limited.[17] Our first task was thus to develop an efficient entry to such pyrrolidines that would provide for the incorporation of butenyl and alkynyl side-chains. We reasoned that a one-pot protocol for preparing *cis*-pyrrolidines could be achieved by the reaction of *N*-acyl pyroglutamates, which are readily available in both enantiomeric forms, with an organometallic reagent followed by the stereoselective hydride reduction of the transient iminium ion that would be generated by ionization of the intermediate *N*,*O*-acetal. Use of a bulky hydride reducing agent would then be expected to preferentially deliver a hydride to the iminium ion from the face opposite the C2-substituent.

In order to test the feasibility of this approach to *cis*-2,5-disubstituted pyrrolidines, a model study was first undertaken employing commercially available L-pyroglutaminol (**2**). In the event, **2** was converted into the imide **3** in excellent overall yield using standard procedures (Scheme 2). We then systematically screened suitable conditions for effecting the one-pot transformation of **3**

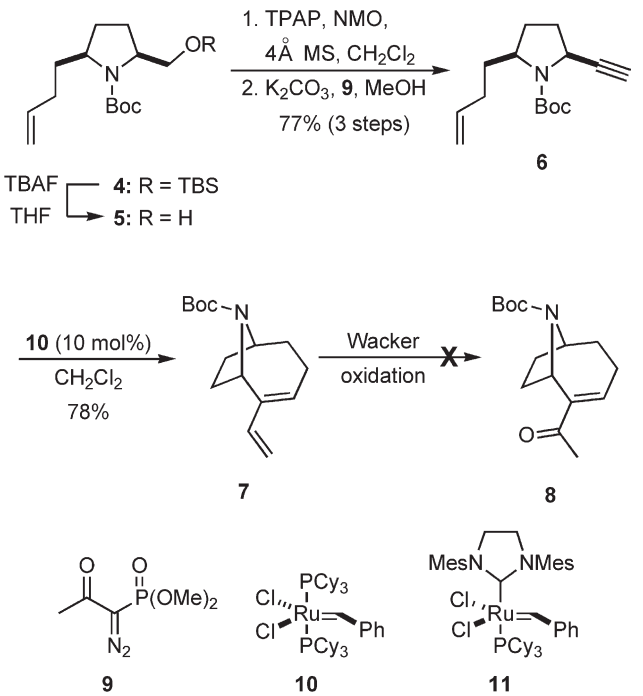


Scheme 2.

into **4**. Thus, reaction of **3** with 3-butenylmagnesium bromide afforded an intermediate alkoxyaminal that was treated in situ with a variety of Lewis acids and sterically demanding hydride donors.[18] We found that the combination of $BF_3{\cdot}OEt_2$ and L-Selectride provided the best yields of the desired *cis*-pyrrolidine **4** with excellent diastereoselectivity (*dr*=31:1).

Although this protocol was effective on smaller scales, attempts to increase the scale of the reaction to prepare gram quantities of **4** resulted in drastically reduced yields. The origin of this problem remains unknown, but we speculated that inefficient cooling during premixing of the $BF_3{\cdot}OEt_2$ and L-Selectride on larger scales may have resulted in the generation of borane.[19] Despite this drawback, these experiments provided sufficient quantities of **4** to explore the feasibility of an enyne metathesis to form a 9-azabicylo[4.2.1]nonane skeleton according to Scheme 1. Optimizing the procedure to prepare *cis*-2,5-disubstituted pyrrolidines would wait for another day.

Removal of the silyl ether protecting group from **4** gave the alcohol **5** (Scheme 3). Oxidation of **5** gave the corresponding aldehyde that was transformed to the terminal acetylene **6** in excellent overall yield using Ohira's diazophosphonate (**9**).[20] When the enyne **6** was treated with the Grubbs first-generation catalyst **10**, the desired bicyclic intermediate **7** was obtained in good yield. Exposure of **6** to the more reactive Grubbs second-generation catalyst **11** resulted in diminished yields of **7** owing to the formation of increased amounts of dimeric product. On the other hand, reaction of **6** with **11** under an atmosphere of ethylene resulted in a cross-metathesis reaction between ethylene and the alkyne to deliver a C2-butadiene as the major product.[21]



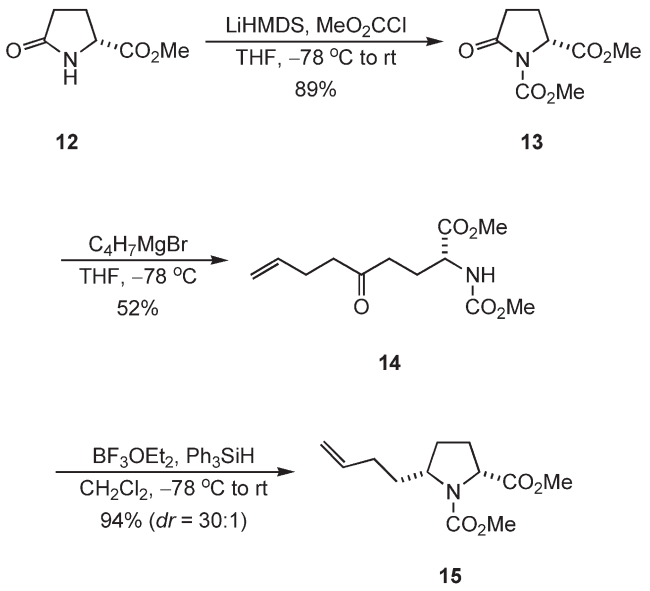
Scheme 3.

We had envisioned that the dienic moiety of **7** would be elaborated into an enone via a Wacker oxidation to deliver

8. However, we recognized that this plan was not supported by a literature precedent as there were no examples of the conversion of conjugated alkenes to enones under Wacker conditions. Rather, in one instance a stable palladium-diene species was isolated and characterized,[22] and in another an oxidative cleavage of a carbon–carbon bond was observed.[23] We were unable to oxidize the exocyclic olefin of **7** to a methyl ketone under a number of different reaction conditions; rather **7** (41–63%) was recovered in all instances.[24] After conducting these experiments, we concluded that the desired conversion of **7** to **8** via a Wacker oxidation would likely not be possible.[25] This realization in conjunction with the variable yields obtained during the one-pot synthesis of the *cis*-pyrrolidine **4** led us to investigate alternative tactics leading to **1**.

Our initial focus was upon developing improved procedures for the synthesis of *cis*-2,5-disubstituted pyrrolidines via the diastereoselective reduction of iminium ions. We were cognizant of several cases wherein the combination of $BF_3{\cdot}OEt_2$ and Et_3SiH was employed to effect the selective reduction of $\Delta^{1,2}$-pyrrolinium ions having a bulky group at the C3-position that directed the facial selectivity of the reduction.[26] We thus envisioned that use of an even more sterically demanding hydride donor such as Ph_3SiH might reduce 2,5-disubstituted-$\Delta^{1,2}$-pyrrolinium ions in a highly diastereoselective fashion from the face opposite the substituent at C5. Such a reduction protocol might also allow for the selective reduction of an *N*-acyl iminium ion in the presence of a C2-ester moiety, thereby allowing more expeditious assembly of a suitable metathesis precursor.

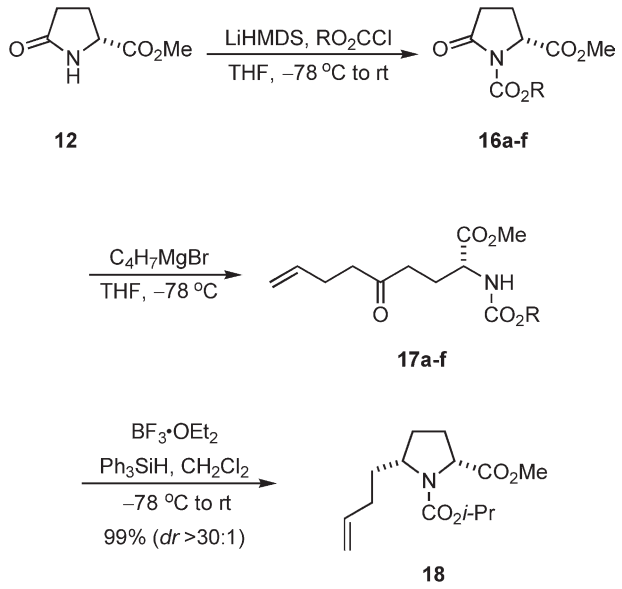
In order to explore the feasibility of the above hypothesis, we directed our attention to preparing **15** according to Scheme 4. D-Methyl-pyroglutamate (**12**) was first converted to the imide **13**, which underwent addition of 3-butenylmagnesium bromide to provide the keto carbamate **14** in modest yield. The remainder of the mass balance was primarily accounted for by the recovery of **12**, which arose from attack of the Grignard reagent on the carbonyl carbon



Scheme 4.

atom of the carbamate moiety.[27] Subsequent treatment of **14** with a premixed solution of $BF_3{\cdot}OEt_2$ and Ph_3SiH provided **15** in 94% yield and excellent diastereoselectivity (*dr*=30:1). Efforts to stream-line the conversion of **13** to **15** into a one-pot process proved problematic, resulting in significantly decreased yields. Therefore, **14** was isolated and purified prior to the cyclization-reduction step.

Stimulated by the successful cyclization/reduction of **14**, we wished to improve the yield of the initial addition step by examining carbamate-protecting groups that would be less susceptible to nucleophilic attack by the Grignard reagent. The series of carbamate derivatives of **16a-f** were thus prepared and treated with 3-butenylmagnesium bromide to afford the keto carbamates **17a-f** (Scheme 5) and the results are tabulated in Table 1.



Scheme 5.

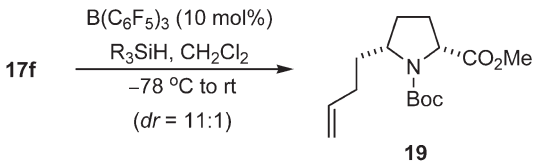
Table 1. Preparation of keto carbamates **17a-f**

Entry	R	Yield (%) **16**	Yield (%) **17**
a	$Cl_3(CH_2)_2$	91	16
b	$(Cl_3C)CMe_2$	95	34
c	Bn	100	44
d	Cyclopentyl	59	59
e	*i*-Pr	84	79
f	*t*-Bu	89	92

As evident by examining Table 1, relatively unhindered or strongly electron withdrawing carbamates were efficiently cleaved in the presence of 3-butenylmagnesium bromide. Only the *i*-propyl and *t*-butyl carbamates **16e**,**f** gave the keto carbamates **17e**,**f** in acceptable yields. When **17e** was treated with $BF_3{\cdot}OEt_2$ and Ph_3SiH, the *cis*-pyrrolidine **18** was isolated in near quantitative yield and >30:1 diastereoselectivity (Scheme 5).

Initial attempts to induce the cyclization/reduction of **17f** using $BF_3{\cdot}OEt_2$ and Ph_3SiH under the same conditions that worked well for transforming **17e** into **18** resulted in extensive loss of the *t*-butyl carbamate moiety. However, we

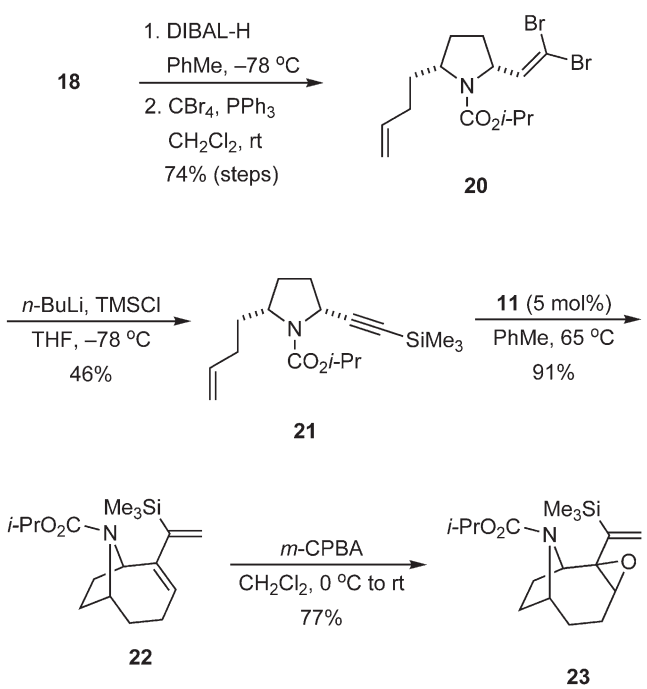
very recently discovered that the cleavage of the *N*-Boc protecting group can be avoided by a modification of our original protocol. Thus, exposure of the keto carbamate **17f** to a premixed solution of Ph_3SiH and $B(C_6F_5)_3$ (10 mol%) afforded **19** in very good diastereoselectivity (*dr*=11:1) and in 98% yield.[28] Inasmuch as the putative reducing agent in this process is the bulky hydridoborate $HB(C_6F_5)_3^-$ ion,[29] we reasoned that Et_3SiH might be used in place of Ph_3SiH as a less expensive and more atom economical hydride source. Supporting this intriguing hypothesis, we discovered that when **17f** was treated with a mixture of Et_3SiH and $B(C_6F_5)_3$ (10 mol%), **19** was obtained in 80% (unoptimized) yield together with a small amount of a lactone that was produced by reduction/cyclization of **17f** (Scheme 6).



Scheme 6.

Returning to the task at hand, it was necessary to develop an efficient means of converting **18** into a substrate for an intramolecular enyne metathesis that would give a product bearing functionality that could be readily elaborated to introduce the methyl ketone moiety found in **1**. In this regard, we had found a simple acetylenic group wanting (vide supra). We thus envisaged that an enyne metathesis involving a TMS-substituted alkyne would give a vinylsilane that could be unmasked to provide the requisite methyl ketone.[30]

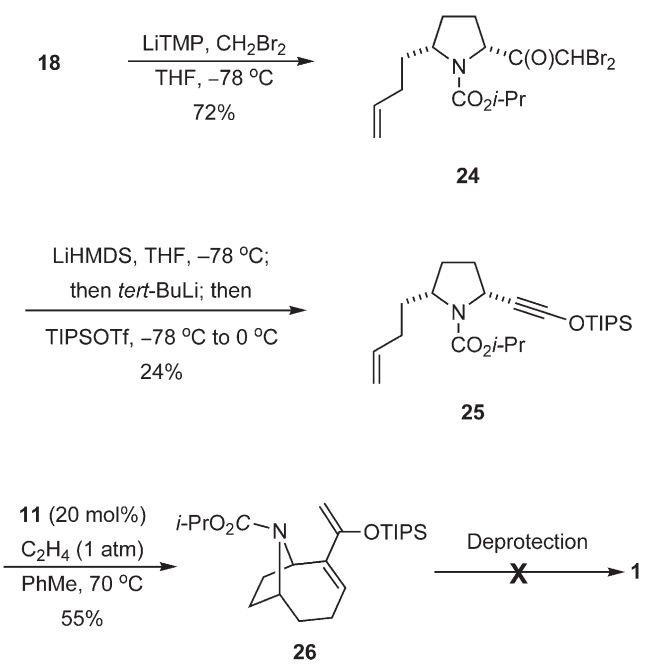
Toward this end, **18** was converted to the dibromo olefin **20** by reducing the ester to an aldehyde with DIBAL-H, followed by Corey-Fuchs olefination (Scheme 7).[31] The dibromide **20** was then converted to the silyl alkyne **21** in modest yield. Exposure of **21** to 5 mol% of **11** provided an excellent yield of the bicyclic vinylsilane **22**.



Scheme 7.

Unfortunately, our plan to convert the vinylsilane moiety of **22** to a methyl ketone by selective epoxidation, followed by an acid-catalyzed hydrolysis and a Peterson elimination was doomed at the outset. Namely, epoxidation of the pendant olefin of **22** with *m*-CPBA furnished the undesired epoxide **23** as the major product contaminated with smaller quantities of a bis-epoxide in a combined 77% yield (10.4:1 ratio respectively). Although an alternative procedure that was developed by Mukaiyama was considered for the hydrolysis of the vinylsilane to the ketone,[32] the operational complexity of the procedure made this option less attractive than a more direct route that we had begun to explore.

During the course of our investigations, Kozmin had reported that the enyne metathesis of siloxy alkynes could be used to synthesize cyclic enones.[33] Encouraged by these results, we queried whether a similar tactic might be employed to provide a silyl enol ether that could be unmasked to reveal the methyl ketone of **1**. We therefore elaborated **18e** to the highly unstable dibromoketone **24** (Scheme 8).



Scheme 8.

Application of the Kowalski protocol for converting **24** to the siloxy alkyne **25** was surprisingly inefficient,[34] and all attempts to optimize the procedure were unsuccessful.

Despite the low yields obtained for the conversion of **24** to **25**, we opted to proceed with the enyne metathesis. Thus, when **25** was exposed to 20 mol% of **11** under an ethylene atmosphere, the desired bicyclic intermediate **26** was isolated in 55% yield. In the absence of ethylene, the reactions required longer reaction times (21 h vs. 5 h) and provided **26** in lower yield (44–46%).

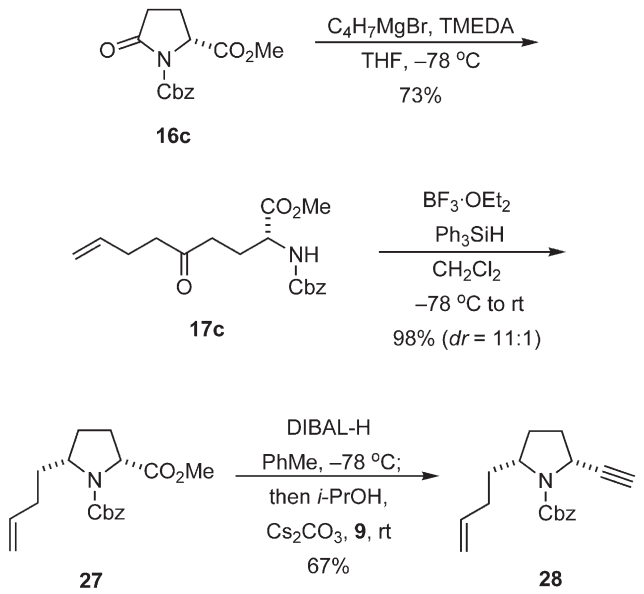
Our intention at this stage was to effect the global deprotection of **26** to arrive at **1**. A survey of the literature revealed but a few examples for removing isopropyl carbamates. The known conditions included exposure to $AlCl_3$,[35] gaseous HF,[36] or to mixtures of H_2SO_4 in TFA.[37] It seemed reasonable that application of these conditions to **26** might simultaneously cleave both the carbamate and silyl-protecting group. Although the silyl enol ether was readily transformed into a methyl ketone under a variety of conditions, the isopropyl carbamate was stable. Attempts to force the reaction under acidic conditions led to decomposition. We explored several other methods used to deprotect carbamates, including *n*-BuLi, Super-Hydride, and basic hydrolysis. We were again unable to remove the carbamate. Owing to the known stability of tertiary isopropyl carbamates, we had anticipated difficulties, but we had optimistically predicted of an eventual success that was not to be. It was thus evident that a more labile carbamate would be required for the synthesis of **1**. Furthermore, the poor yield obtained for the conversion of **24** to **25** signaled that an alternative strategy for the synthesis of a functionalized bicyclic intermediate suitable for conversion to **1** was essential.

The requirement for a hindered carbamate moiety was dictated by a lack of selectivity in the additions of organometallic reagents to *N*-alkoxycarbonyl pyroglutamate derivatives. A practical solution to that vexing problem was discovered in the context of methodological studies directed toward developing improved routes to *cis*-2,5-disubstituted pyrrolidines. In particular, we discovered that the yields of the additions of Grignard reagents to *N*-alkoxycarbonyl pyroglutamates was significantly improved by premixing the organometallic reagent with an excess of *N*,*N*,*N*′,*N*′-TMEDA.[38] Under these conditions, competing nucleophilic attack on the carbonyl carbon atom of the carbamate moiety was reduced dramatically. It remained to validate this tactic in our synthesis of (+)-anatoxin-a.

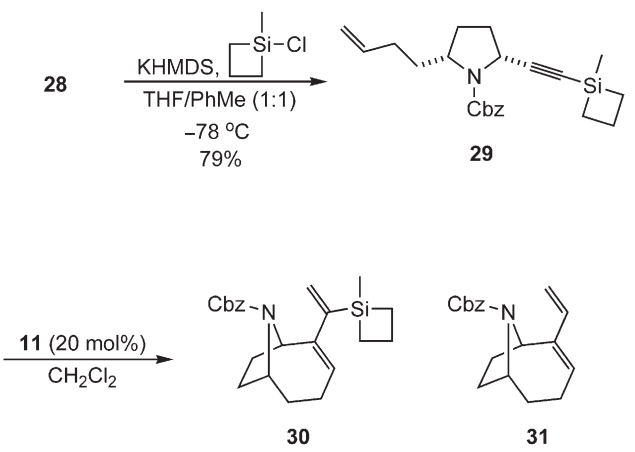
In the event, treating **16c** with a premixed solution of 3-butenylmagnesium bromide and TMEDA afforded the keto carbamate **17c** in 73% yield as contrasted with a yield of 44% in previous experiments (Scheme 9). The **17c** thus obtained was cyclized and reduced with $BF_3{\cdot}OEt_2$ and Ph_3SiH as before to afford the *cis*-pyrrolidine **27** in 99% yield (*dr*=11:1). A one-pot reduction–homologation procedure, which had been developed within our group,[8b] was performed to obtain the enyne **28**. At this stage the minor *trans*-diastereomer (6%) was removed by flash chromatography to provide pure **28**.

It was recently reported that vinyl silacyclobutanes may be oxidatively converted to ketones.[39] We therefore envisioned a new strategy for the synthesis of **1** that involved the enyne metathesis of an alkynyl silacyclobutane to give a vinyl siletane that could be elaborated to a methyl ketone under mild conditions (Scheme 10). Supporting our idea was an example of a ruthenium catalyzed RCM involving a silacyclobutane.[40]

Encouraged by these findings, we converted **28** to the enyne metathesis precursor **29** (Scheme 10). Attempts to induce



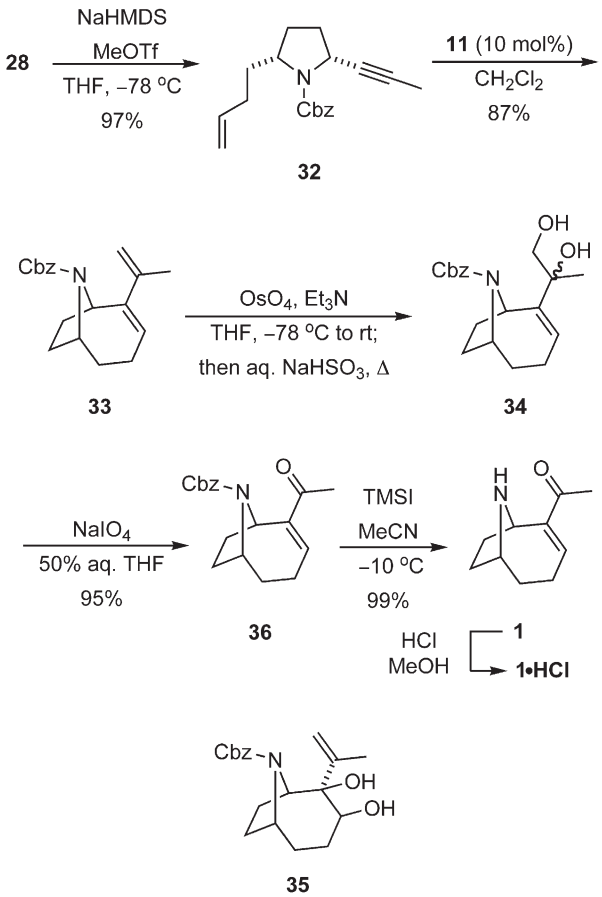
Scheme 9.



Scheme 10.

the enyne metathesis of **29** in the presence of **11** (20 mol%) at room temperature failed to provide any of the desired bicycle **30**; rather **29** (73%) was recovered along with a small amount of the protodesilylated material **31** (4%). When the reaction was performed at 80 °C (sealed tube), **31** (76%) was isolated along with smaller quantities of **29** (8%) and **28** (9%), indicating that the silacyclobutane moiety was labile under these conditions. The mechanistic pathway by which the desilylation occurs is unclear, but it is possible that oxidative insertion of the ruthenium alkylidene species into the silacyclobutane might be responsible.[41]

It was again time to explore other variations of an enyne metathesis that would lead to (+)-anatoxin-a (**1**). The plan for what was to be our final attempt was predicated on the hypothesis that it should be possible to induce the selective oxidative cleavage of a diene such as **33** to generate the elusive methyl ketone moiety in **1** (Scheme 11). Toward this end, **29** was first deprotonated with LDA and the resulting lithium acetylide was trapped with MeI or MeOTf. However, the yield of **32** was poor owing to competing



Scheme 11.

deprotection of the Cbz-group. This problem was, however, readily circumvented by alkylation of the corresponding sodium acetylide with MeOTf to furnish **32** in excellent yield. When the enyne **32** was exposed to 10 mol% of **11**, the bicyclic diene **33** was obtained in 91% yield.

The critical stage was then set for selectively converting the pendant isopropenyl group present in **33** to a methyl ketone moiety via an oxidative cleavage. Previous work in our laboratories with a related system suggested that a Sharpless asymmetric dihydroxylation[42] followed by diol cleavage would be superior to ozonolysis for effecting this transformation.[8b] However, we found that oxidation of **33** using AD-mix β gave a mixture of diols **34** and **35** from which the desired enone **36** was obtained in only 57% yield. Worse yields arose from the use of AD-mix α, presumably because of a chiral mismatch.

We then examined the utility of the complexes generated by mixing OsO_4 with amines. Corey had found that enantioselective dihydroxylations could be induced with OsO_4 in the presence of chiral diamines.[43] Even though such a tactic would require use of stoichiometric amounts of OsO_4, we reasoned that the increased steric bulk about osmium in these complexes would favor dihydroxylating the more accessible isopropenyl group. Although treating **33** with the complex generated from OsO_4 and TMEDA resulted in complete recovery of **33**, reaction of **33** with the complex of OsO_4 and quinuclidine provided **34** in 74% yield along with the regioisomeric diol **35** (11%). Because quinuclidine is rather expensive, we screened several other tertiary amines and discovered that the complex generated from OsO_4 and Et_3N provided **34** (76%) together with **35** (13%). This mixture of diols was readily separated by flash chromatography to afford pure **34** that was subsequently cleaved by periodate ion to deliver Cbz-anatoxin-a **36**.[44] *N*-Deprotection of **36** by the action of TMSI at −10 °C furnished **1** in nearly quantitative yield. The free base thus obtained was then converted into its more stable hydrochloride salt to prevent light-induced decomposition.[45] The spectral and physical data obtained for synthetic **1** and its hydrochloride salt were consistent with those reported by Rapoport.[44,46]

3. Conclusions

In summary, we have completed a concise and practical synthesis of the potent neurotoxic alkaloid (+)-anatoxin-a (**1**) in a sequence of only nine chemical operations and in 27% overall yield from commercially available **12**. The strategy featured the application of a new protocol for the diastereoselective synthesis of *cis*-2,5-disubstituted pyrrolidines bearing unsaturated side chains and an intramolecular enyne metathesis to provide the requisite azabicyclo[4.2.1]-nonane skeleton of **1**. We also developed an improvement to our method for the cyclization/reduction of keto carbamates derived from pyroglutamic acid in which catalytic amounts of $B(C_6F_5)_3$ and silanes are employed to reduce transient iminium ions. We are currently exploring the scope of this new reagent combination for the stereoselective reduction of oxonium and iminium ions. Significantly, the approach is versatile and may be applied to the facile preparation of nonlethal analogs of **1** by simply modifying the nature of the unsaturated side-chains at the 2- and 5-positions of the *cis*-pyrrolidine ring prior to metathesis. We are in the process of developing new applications of intramolecular enyne metathesis and related processes for the synthesis of alkaloid natural products, the results of which will be reported in due course.

4. Experimental

4.1. General

Solvents and reagents were reagent-grade and were used without purification, unless otherwise noted. Dichloromethane (CH_2Cl_2), *N*,*N*,*N*′*N*′-tetramethylethylene-diamine (TMEDA), and diisopropylamine were distilled from calcium hydride and stored under nitrogen. Boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) was distilled from calcium hydride. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were passed through two columns of neutral alumina and stored under argon. Methanol (MeOH) and acetonitrile (MeCN) was passed through two columns of molecular sieves and stored under argon. Toluene were first passed through a column neutral alumina, then through a column of Q5 reactant and stored under argon. Iodotrimethylsilane (TMSI) was freshly distilled over flame-dried copper powder onto the same under argon, in the absence of light. All reactions were performed in flame-dried glassware under argon unless otherwise noted. All metatheses were performed in freshly distilled solvent, degassed with a

continuous stream of argon for a minimum of 15 min. All reaction temperatures are reported as the temperature of the surrounding bath. ^{1}H nuclear magnetic resonance (NMR) spectra were obtained at 500 or 400 MHz as solutions in DMSO-d_6 or $CDCl_3$ unless otherwise noted. ^{13}C NMR spectra were obtained at 125 MHz or 100 MHz as solutions in DMSO-d_6 or $CDCl_3$ unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ) and referenced to the solvent. Coupling constants are reported in Hertz (Hz). Spectral splitting patterns are designated as s: singlet, d: doublet, t: triplet: q: quartet, m: multiplet, comp m: complex multiplet, br: broad. Infrared (IR) spectra were obtained using a Perkin–Elmer FTIR 1600 spectrophotometer. IR spectra were taken neat on sodium chloride plates unless otherwise noted and reported in wave numbers (cm^{-1}). Low-resolution chemical ionization (CI) mass spectra were obtained with a Finnigan TSQ-70 instrument. High-resolution measurements were made with a VG Analytical ZAB2-E instrument. Analytical thin layer chromatography was performed using Merck 250 micron 60F-254 silica gel plates. The plates were visualized with ultraviolet (UV) light, potassium permanganate ($KMnO_4$), ammonium molybdate ceric ammonium nitrate (AmCAN), or ceric ammonium molybdate (CAM/Hanessians stain). Flash chromatography was performed according to the method of Still[47] using ICN Silitech 32-63 D 60A silica gel, Aldrich Activated Brockmann I, standard grade, 150 mesh. D-methylpyroglutamate (**12**) was prepared according to the procedure of Pfaltz.[48] Compound **16f** was prepared from **12** according to the method of Tamm.[49] Compound **3** was prepared from **2** according to the procedure of Konas.[50] Compounds **16a-e** were prepared from **12** using the method of Kikugawa.[51] (1-Diazo-2-oxo-propyl)phosphonic acid dimethyl ester (**9**) was prepared according to the procedure of Vandewalle.[52]

4.1.1. (2*S*)-But-3-enyl-(5*S*)-(*tert*-butyldimethylsilanoxylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (4). 4-Bromo-1-butene (18 μL, 0.18 mmol) was added to a stirred mixture of magnesium turnings (26 mg, 1.1 mmol) in THF (1.1 mL) at room temperature. After 20 min, an additional portion of 4-bromo-1-butene (40 μL, 0.35 mmol) was added. The resulting solution was stirred an additional 20 min and then transferred via cannula to a stirred solution of **3** (89 mg, 0.27 mmol) in THF (1.4 mL) at −78 °C. The mixture was stirred for 1 h at −78 °C, and then a mixture of $BF_3{\cdot}OEt_2$ (0.22 mL, 1.7 mmol) and 1 M L-Selectride in THF (0.57 mL, 0.57 mmol) (mixed at room temperature) was added via syringe. The resulting solution was stirred at −78 °C for 1 h, and then the solution was allowed to slowly warm to room temperature before quenching with MeOH (2.5 mL) and H_2O (3 mL). The reaction mixture was then poured into a mixture of saturated $NaHCO_3$ (30 mL) and Et_2O/pentane (1:1) (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O/pentane (1:1) (3×15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:5) to provide 79 mg (79%) of **4** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85–5.75 (m, 1H), 5.00 (dq, J=17.4, 1.7 Hz, 1H), 4.94 (app d, J=9.9 Hz, 1H), 3.76–3.36 (comp, 4H), 2.14–1.72 (comp, 5H), 1.68–1.52 (m, 1H), 1.44 (s, 9H), 0.87 (s, 9H), 0.03 (d, J=3.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 138.6, 114.6, 79.5, 60.4, 57.1, 40.6, 31.6, 29.4, 26.8, 26.5, 19.2, −4.2; IR (neat) 3446, 2941, 1696, 1460, 1393, 1365, 1258, 1174, 1101, 837, 776; mass spectrum (CI) m/z 370.2777 [$C_{20}H_{40}NO_3Si$ (M+1) requires 370.2778], 370, 314, 298, 270 (base), 256.

4.1.2. (2*S*)-But-3-enyl-(5*S*)-hydroxymethylpyrrolidine-1-carboxylic acid *tert*-butyl ester (5). A 1 M solution of TBAF in THF (6.2 mL, 6.20 mmol) was added to a stirred solution of **4** (521 mg, 1.41 mmol) in THF (8 mL). The mixture was stirred for 2 h, and then poured into 10% H_3PO_4 (50 mL) and EtOAc (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×20 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an orange oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (2:3) to afford 250 mg (70%) of **5** as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, J=17.1, 10.2, 6.6 Hz, 1H), 5.00 (dq, J=15.5, 1.6 Hz, 1H), 4.94 (br dq, J=8.4, 1.8 Hz, 1H), 3.96–3.90 (m, 1H), 3.87–3.81 (m, 1H), 3.65 (br dd, J=8.6, 2.4 Hz, 1H), 3.49 (dd, J=11.2, 7.9 Hz, 1H), 2.11–1.93 (comp, 3H), 1.90–1.80 (m, 1H), 1.77–1.50 (comp, 3H), 1.45 (s, 9H), 1.42–1.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 114.8, 80.4, 68.8, 61.1, 58.8, 34.6, 30.7, 28.9, 28.5, 26.9; IR (neat) 3416, 3074, 2967, 1693, 1661, 1399, 1255, 1170, 1116, 1047, 908, 855, 775, 737 cm^{-1}; mass spectrum (CI) m/z 256.1919 [$C_{14}H_{26}NO_3$ (M+1) requires 256.1913], 511, 411, 379, 256 (base), 224, 200, 184, 156.

4.1.3. (2*S*)-But-3-enyl-(5*S*)-formylpyrrolidine-1-carboxylic acid *tert*-butyl ester. TPAP (33 mg, 0.094 mmol) was added to a solution of **5** (239 mg, 0.936 mmol), NMO (165 mg, 1.40 mmol), and powdered 4 Å molecular sieves (300 mg) in CH_2Cl_2 (31 mL) at room temperature. The reaction was stirred for 2 h, and then the solvent was removed under reduced pressure to afford a black residue. The residue was suspended in Et_2O (2 mL), and filtered through a short plug of SiO_2 eluting with Et_2O/pentane (2:1) (175 mL). Removal of the solvent under reduced pressure afforded 216 mg (91%) of the aldehyde as a pale-yellow oil. ^{1}H NMR (500 MHz, PhMe-d_8, 100 °C) δ 9.35 (d, J=2.4 Hz, 1H), 5.73 (ddt, J=16.7, 10.2, 6.3 Hz, 1H), 4.97 (dq, J=17.1, 1.7 Hz, 1H), 4.91–4.88 (m, 1H), 3.93–3.90 (m, 1H), 3.78–3.71 (m, 1H), 2.02–1.81 (comp, 3H), 1.60–1.42 (comp, 3H), 1.37 (s, 9H), 1.30–1.19 (comp, 2H); ^{13}C NMR (125 MHz, PhMe-d_8, 100 °C) δ 199.1, 154.7, 138.6, 114.8, 80.2, 66.6, 58.8, 35.0, 30.9, 30.0, 28.6, 25.4; IR (neat) 2974, 1739, 1696, 1455, 1382, 1258, 1168, 1112, 910, 776 cm^{-1}; mass spectrum (CI) m/z 254.1765 [$C_{14}H_{24}NO_3$ (M+1) requires 254.1756], 254, 238, 226, 224, 198 (base), 182, 180, 155, 136, 124.

4.1.4. (2*S*)-But-3-enyl-(5*S*)-ethynylpyrrolidine-1-carboxylic acid *tert*-butyl ester (6). A solution of the proceeding aldehyde (207 mg, 0.817 mmol) in anhydrous MeOH (1 mL) was added via syringe to a solution of **9** (188 mg, 0.981 mmol) and K_2CO_3 (226 mg, 1.63 mmol) in anhydrous MeOH (6 mL) at room temperature. The reaction was stirred for 3 h, and then diluted with Et_2O (6 mL) and poured into a mixture of saturated $NaHCO_3$ (25 mL) and

Et_2O (5 mL). The layers were separated and the aqueous phase was extracted with Et_2O (4×15 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an pale-yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:6) to afford 155 mg (76%) of **6** as a clear oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 5.84 (ddt, J=16.8, 10.2, 6.5 Hz, 1H), 5.03 (dq, J=17.2, 1.7 Hz, 1H), 4.96–4.92 (m, 1H), 4.47–4.43 (m, 1H), 3.77–3.72 (m, 1H), 2.89 (d, J=2.1 Hz, 1H), 2.13–1.96 (comp, 4H), 1.93–1.85 (comp, 2H), 1.78–1.71 (m, 1H), 1.57–1.49 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 152.7, 137.8, 113.8, 84.9, 78.3, 71.0, 57.0, 47.7, 33.4, 31.1, 29.0, 28.9, 27.6; IR (neat) 3302, 3059, 2978, 1685, 1639, 1390, 1263, 1170, 1107, 916, 737, 650 cm^{-1}; mass spectrum (CI) m/z 250.1807 [$C_{15}H_{24}NO_2$ (M+1) requires 250.1807], 499, 444, 399, 343, 250 (base), 194.

4.1.5. 2-Vinyl-9-azabicyclo[4.2.1]non-2-ene-9-carboxylic acid *tert*-butyl ester (7). To a solution of **6** (18 mg, 72 μmol) in dry degassed CH_2Cl_2 (8 mL) was added **10** (7 mg, 0.008 mmol) in one portion. The mixture was stirred at room temperature for 22 h, and then DMSO (1 mL) was added to decompose the catalyst, and stirring was continued for an additional 2 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (SiO_2) using gradient elution Et_2O/pentane (1:5→1:3) to afford 14 mg (78%) of **7** as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) (2 rotamers) δ 6.23 (dd, J=17.6, 6.6 Hz, 1H), 5.65–5.60 (m, 1H), 5.14 (t, J=17.1 Hz, 1H), 4.98–4.90 (comp, 1.4H), 4.80–4.77 (m, 0.6H), 4.40–4.37 (m, 0.6H), 4.28–4.24 (m, 0.4H), 2.32–2.02 (comp, 5H), 1.77–1.65 (comp, 2H), 1.62–1.51 (comp, 2H), 1.44 (s, 4H), 1.39 (s, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) (2 rotamers) δ 153.5, 153.3, 145.9, 143.8, 139.0, 138.8, 131.2, 130.8, 111.3, 110.5 79.1, 79.0, 55.2, 54.8, 54.3, 33.9, 31.9, 31.4, 31.0, 30.4, 30.3, 29.6, 28.6, 28.5, 23.8, 23.6; IR (neat) 3437, 2978, 2252, 1683, 1420, 1405, 1367, 1250, 1170, 1116, 994, 908, 737, 652 cm^{-1}; mass spectrum (CI) m/z 250.1803 [$C_{15}H_{24}NO_2$ (M+1) requires 250.1807], 250 (base), 222, 200, 195, 152.

4.1.6. (2*R*)-Methoxycarbonylamino-5-oxonon-8-enoic acid methyl ester (14). 4-Bromo-1-butene (72 μL, 0.71 mmol) was added to a stirred mixture of magnesium turnings (202 mg, 8.32 mmol) in THF (8.3 mL) at room temperature. The mixture was stirred for 10 min, and an additional portion of 4-bromo-1-butene (350 μL, 3.45 mmol) was added. The resulting mixture was stirred for an additional 15 min and then transferred via syringe to a flask containing TMEDA (3.8 mL, 25 mmol). The initially cloudy suspension was stirred until all precipitate had disappeared (5 min), whereupon the solution was transferred via syringe to a solution of **13** (558 mg, 2.77 mmol) in THF (14 mL) at −78 °C. The reaction mixture was stirred for 1.5 h at −78 °C, and MeOH (5 mL) was added. The reaction mixture was then poured into a mixture of 10% H_3PO_4 (50 mL) and Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3×20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (2:1) to provide 465 mg (65%) of **14** as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (ddt, J=16.8, 10.3, 6.5 Hz, 1H), 5.29 (br s, 1H), 5.04–4.93 (comp, 2H), 4.30 (m, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 2.60–2.40 (comp, 4H), 2.34–2.25 (comp, 2H), 2.33–2.26 (m, 1H), 1.96–1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 172.5, 156.6, 136.8, 115.2, 53.2, 52.3, 52.2, 41.6, 38.3, 27.5, 26.0; IR (neat) 3345, 2952, 1713, 1640, 1528, 1443, 1359, 1264, 1219, 1062, 1000, 916, 781 cm^{-1}; mass spectrum (CI) m/z 258.1348 [$C_{12}H_{20}NO_5$ (M+1) requires 258.1342], 258, 240 (base), 226, 198.

4.1.7. (2*R*,5*R*)-But-3-enylpyrrolidine-1,2-dicarboxylic acid dimethyl ester (15). $BF_3{\cdot}OEt_2$ (5.50 mL, 43.2 mmol) was added to a solution of Ph_3SiH (5.63 g, 21.6 mmol) in CH_2Cl_2 (14 mL) at room temperature. The solution was stirred for 5 min, and then transferred via cannula to a stirred solution of **14** (1.85 g, 7.21 mmol) in CH_2Cl_2 (24 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 0.5 h, whereupon the cooling-bath was removed and stirring was continued at room temperature for an additional 2 h. The reaction mixture was recooled to −78 °C and poured into a mixture of sat. aqueous $NaHCO_3$ (40 mL) and CH_2Cl_2 (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3×20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a clear oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (3:1) to provide 1.62 g (93%) of **15** as a clear oil (*dr*=16:1)[53]. ^{1}H NMR (500 MHz, $CDCl_3$) (2 rotamers) δ 5.90–5.78 (m, 1H), 5.05 (app dd, J=17.3, 1.8 Hz, 1H), 4.96 (br d, J=9.8 Hz, 1H), 4.42–4.30 (m, 1H), 4.01–8.85 (m, 1H), 3.77–3.63 (comp, 6H), 2.26–2.16 (m, 1H), 2.14–1.90 (comp, 5H), 1.78–1.68 (m, 1H), 1.58–1.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (2 rotamers) δ 173.4, 155.6, 155.0, 138.1, 137.9, 114.7, 114.6, 60.0, 59.6, 58.8, 58.1, 52.4, 52.1, 33.5, 33.1, 30.5, 30.0, 29.3, 29.1, 28.1; IR (neat) 2955, 1754, 1704, 1450, 1385, 1202, 1175, 1112, 1000, 912, 773 cm^{-1}; mass spectrum (CI) m/z 242.1388 [$C_{12}H_{20}NO_4$ (M+1) requires 242.1392], 242 (base), 210, 186, 168.

4.1.8. (2*R*)-Isopropoxycarbonylamino-5-oxonon-8-enoic acid methyl ester (17e). 4-Bromo-1-butene (0.70 mL, 6.9 mmol) was added to a stirred mixture of magnesium turnings (1.3 g, 52 mmol) in THF (55 mL) at room temperature. The mixture was stirred for 10 min, and an additional portion of 4-bromo-1-butene was added (2.0 mL, 20 mmol). The resulting mixture was stirred for an additional 1 h, whereupon the solution was transferred via cannula to a solution of **16e** (2.0 g, 8.7 mmol) in THF (65 mL) at −78 °C over a 1 h period. Stirring was continued for an additional 1 h at −78 °C, whereupon a solution of sat. NH_4Cl (10 mL) was added. The reaction mixture was then poured into a mixture of brine (100 mL) and EtOAc (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3×50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (1:2) to provide 1.9 g (77%) of **17e** as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83–5.75 (ddt, J=16.9, 10.2, 6.6 Hz, 1H), 5.22 (br d, J=6.6 Hz, 1H), 5.02 (ddd, J=17.1, 3.4, 1.6 Hz, 1H), 4.97 (ddd, J=10.2, 3.0, 1.4 Hz, 1H), 4.89 (hept, J=6.0 Hz, 1H), 4.32 (br d, J=5.0 Hz, 1H), 3.74 (s, 3H),

2.59–2.46 (comp, 4H), 2.35–2.30 (comp, 2H), 2.20–2.11 (m, 1H), 1.96–1.88 (m, 1H), 1.23 (d, J=6.3 Hz, 3H), 1.21 (d, J=6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); 208.7, 172.7, 155.8, 136.9, 115.3, 68.6, 53.1, 52.4, 41.8, 38.4, 27.6, 26.4, 22.1, 22.0; IR (neat) 3349, 3077, 2981, 1714, 1642, 1524, 1438, 1375, 1209, 1180, 1112, 1043 cm^{-1}; mass spectrum (CI) m/z 286.1652 [$C_{14}H_{24}NO_5$ (M+1) requires 286.1654], 286 (base), 268, 244, 226, 200, 182, 144.

4.1.9. (2*R*,5*R*)-1-Isopropyl-2-methyl-5-(but-3-enyl)-pyrrolidine-1,2-dicarboxylate (18). A solution of $BF_3{\cdot}OEt_2$ (2.7 mL, 21 mmol) and Ph_3SiH (2.7 g, 11 mmol) in CH_2Cl_2 (5 mL) was added via syringe to a stirred solution of **17e** (1.0 g, 3.5 mmol) in CH_2Cl_2 (25 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 0.5 h, whereupon the cooling-bath was removed and stirring was continued at room temperature for an additional 2 h. The reaction mixture was recooled to −78 °C and poured into a mixture of sat. aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (10 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a clear oil. The crude product was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (1:4) to provide 941 mg (99%) of **18** (dr >30:1)[53] as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) (2 rotamers) δ 5.86–5.79 (m, 1H), 5.05–5.02 (m, 1H), 5.00–4.85 (comp, 2H), 4.40–4.24 (m, 1H), 3.98–3.83 (m, 1H), 3.72 (s, 3H), 2.27–1.89 (comp, 6H), 1.79–1.72 (m, 1H), 1.59–1.44 (m, 1H), 1.27–1.12 (comp, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) (2 rotamers) δ 173.7, 173.6, 154.8, 154.1, 138.2, 114.5, 68.7, 68.4, 59.8, 59.7, 59.4, 58.5, 57.8, 52.0, 33.7, 33.0, 30.7, 30.5, 30.1, 29.2, 28.9, 28.1, 22.3, 22.2, 22.1, 21.9; IR (neat) 2978, 2952, 1753, 1699, 1640, 1436, 1404, 1385, 1315, 1202, 1175, 1113, 998 cm^{-1}; mass spectrum (CI) m/z 270.1709 [$C_{14}H_{24}NO_4$ (M+1) requires 270.1705], 270 (base), 228, 210, 184, 168, 128.

4.1.10. (2*R*)-1-*tert*-Butoxycarbonylamino-5-oxonon-8-enoic acid methyl ester (17f). A two-neck flask was charged with magnesium turnings (200 mg, 8.26 mmol) and THF (8 mL). To this stirred mixture was added a portion of 4-bromo-1-butene (0.10 mL, 0.99 mmol) at room temperature. After 15 min, an additional portion of 4-bromo-1-butene (0.32 mL, 3.15 mmol) was added. The resulting yellow solution was stirred for 10 min and then transferred via cannula to a stirred solution of **16f** (502 mg, 2.06 mmol) in THF (14 mL) at −78 °C. The mixture was stirred for 3 h at −78 °C, and then saturated NH_4Cl (5 mL) was added and the reaction mixture was poured into a mixture of H_2O (60 mL) and Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3×20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (1:2) to provide 570 mg (92%) of **17f** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83–5.68 (m, 1H), 5.12–4.75 (comp, 3H), 4.28–4.17 (m, 1H), 3.70–3.67 (comp, 3H), 2.57–2.37 (comp, 4H), 2.31–2.24 (comp, 2H), 2.14–2.03 (m, 1H), 1.99–1.78 (m, 1H), 1.40–1.37 (comp, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 173.1, 155.7, 137.2, 115.6, 80.2, 53.1, 52.6, 42.1, 38.7, 28.5, 27.9, 26.7; IR (neat) 3465, 3064, 2984, 1741, 1707, 1392, 1363, 1169, 733 cm^{-1}; mass spectrum (CI) m/z 300.1805 [$C_{15}H_{26}NO_5$ (M+1) requires 300.1811], 300, 282, 244 (base), 200, 182.

4.1.11. (2*R*,5*R*)-1-*tert*-Butyl-2-methyl-5-(but-3-enyl)-pyrrolidine-1,2-dicarboxylate (19). $B(C_6F_5)_3$ (8.2 mg, 0.02 mmol) was added to a solution of Ph_3SiH (92 mg, 0.35 mmol) in CH_2Cl_2 (1 mL) at room temperature. The solution was stirred for 10 min, and then added via cannula to a stirred solution of **17f** (48 mg, 0.16 mmol) in CH_2Cl_2 (0.5 mL) at −78 °C. The mixture was maintained in a −78 °C bath for 0.5 h, whereupon the cooling-bath was removed, and stirring was continued at room temperature for an additional 2 h. The mixture was then recooled to −78 °C and an additional 1 mL of a pre-mixed solution of $B(C_6F_5)_3$ (8.2 mg, 0.02 mmol) and Ph_3SiH (92 mg, 0.35 mmol) was added via cannula. The solution was stirred at −78 °C for 10 min, and then the cooling bath was removed and stirring was continued at room temperature for 11 h. Et_3N (0.1 mL) was added and stirring was continued for 20 min. The mixture was poured into a solution of 10% H_3PO_4 (20 mL) and Et_2O (5 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×8 mL). The combined organic layers were dried ($MgSO_4$), filtered through a 2 cm plug of SiO_2 with Et_2O (40 mL), and concentrated under reduced pressure to afford a pale-yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:1) to provide 44 mg (97%) of **19** (dr=11:1, by ^{1}H NMR) as a clear oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 5.84 (ddt, J=17.0, 10.2, 6.6 Hz, 1H), 4.98 (app dq, J=17.2, 1.7 Hz, 1H), 4.96–4.93 (m, 1H), 4.21 (t, J=7.5 Hz, 1H), 3.82–3.77 (m, 1H), 3.65 (s, 2.76H, major diast.), 3.64 (s, 0.24H, minor diast.) 2.20–1.83 (comp, 6H), 1.70–1.65 (m, 1H), 1.52–1.44 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 172.6, 152.7, 138.0, 113.8, 78.4, 59.1, 57.3, 50.9, 32.7, 29.4, 28.7, 27.6; IR(neat) 2974, 1754, 1697, 1390, 1172, 1115, 710, 513; mass spectrum (CI) m/z 284.1860 [$C_{15}H_{26}NO_4$ (M+1) requires 284.1862], 284 (base), 228, 184.

4.1.12. (2*R*,5*S*)-5-But-3-enyl-2-(2,2-dibromovinyl)-pyrrolidine-1-carboxylic acid isopropyl ester (20). A 1.0 M solution of DIBAL-H in toluene (1.6 mL, 1.6 mmol) was added dropwise to a solution of **18** (393 mg, 1.46 mmol) in toluene (4 mL) at −78 °C. After 1 h at −78 °C, an additional portion of DIBAL-H (1.6 mL, 1.6 mmol) was added, and the mixture was stirred at −78 °C for 15 min. MeOH (0.5 mL) was added, and the mixture was poured into a solution of saturated Rochelle's salt (11 mL) and EtOAc (10 mL), The mixture was stirred at room temperature until the layers separated (1.5 h). The mixture was then poured into brine (20 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3×15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow oil. The crude product was purified by flash chromatography (neutral Al_2O_3) eluting with EtOAc/hexanes (1:4) to provide 277 mg (79%) of the aldehyde as a pale-yellow oil that was used immediately in the next reaction.

A solution of CBr_4 (420 mg, 1.26 mmol) and PPh_3 (662 mg, 2.52 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C. After 20 min, a solution of the proceeding aldehyde (151 mg, 0.631 mmol) in CH_2Cl_2 (1 mL) was added. The reaction

mixture was stirred with warming to room temperature for 29 h in the dark. The resulting slurry was concentrated in vacuo, diluted in a minimal amount of CH_2Cl_2 (1 mL), and purified by flash chromatography (neutral Al_2O_3) eluting with Et_2O/pentane (1:4) to provide 217 mg (87%) of **20** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44–6.20 (m, 1H), 5.88–5.72 (m, 1H), 5.07–4.82 (comp, 3H), 4.52–4.31 (m, 1H), 3.96–3.76 (m, 1H), 2.25–1.29 (comp, 8H), 1.27–1.18 (comp, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 140.9, 138.3, 115.0, 83.3, 68.7, 60.6, 32.3, 30.8, 30.6, 29.4, 22.6, 22.4; mass spectrum (CI) *m*/*z* 396 (M+1) (base), 382, 354, 340, 294, 210.

4.1.13. (2*R*,5*S*)-5-But-3-enyl-2-trimethylsilanylethynyl-pyrrolidine-1-carboxylic acid isopropyl ester (21). A 2.0 M solution of *n*-BuLi (0.44 mL, 8.8 mmol) in hexanes was added to a solution of **20** (165 mg, 0.418 mmol) in THF (5 mL) at −78 °C. The mixture was stirred for 1.5 h at −78 °C, and then TMSCl (60 μL, 0.46 mmol) was added. The solution was stirred at −78 °C for 4.5 h, and then phosphate buffer (pH 7.4) (1 mL) was added and the reaction was poured into a mixture of brine (10 mL) and Et_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3×15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a dark-yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:6) to provide 59 mg (46%) of **21** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88–5.74 (m, 1H), 5.06–4.85 (comp, 3H), 4.61–4.42 (m, 1H), 3.89–3.76 (m, 1H), 2.16–1.50 (comp, 8H), 1.25–1.20 (comp, 6H), 0.13–0.09 (comp, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 138.4, 114.4, 86.1, 68.3, 57.8, 49.2, 34.1, 32.2, 30.1, 22.3, −0.01; mass spectrum (CI) *m*/*z* 308 (M+1) (base), 292, 266.

4.1.14. 2-(1-Trimethylsilanylvinyl)-9-azabicyclo[4.2.1]-non-2-ene-9-caboxylic acid isopropyl ester (22). A solution of **21** (26 mg, 0.085 mmol) in degassed PhMe (0.85 mL) was treated with one portion of solid **11** (4 mg, 4 μmol), and then the solution was sparged for an additional 10 min. The mixture was then heated to 65 °C for 14 h. After cooling to room temperature, the solution was allowed to stir for 2 h exposed to the atmosphere, and then the solvent was removed under reduced pressure to afford a crude brown oil that was purified by flash chromatography (SiO_2) using gradient elution with hexanes and then EtOAc/hexanes (1:5) to afford 24 mg (91%) of **22** as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60–5.31 (comp, 2H), 4.97–4.84 (m, 1H), 4.62–4.38 (br m, 1H), 3.92–3.72 (br m, 1H), 2.68–2.45 (m, 1H), 2.34–2.13 (m, 1H), 2.12–1.75 (comp, 4H), 1.66–1.59 (dd, *J*=6.3, 2.1 Hz, 3H), 1.26–1.19 (app dd, *J*=6.4, 3.6 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 154.4, 148.2, 127.6, 126.5, 68.2, 57.3, 49.5, 36.4, 31.3, 29.7, 22.3, 22.2, 18.0, −0.1; mass spectrum (CI) *m*/*z* 308 (M+1), 292, 264 (base), 238, 179.

4.1.15. (2*R*,5*S*)-5-But-3-enyl-2-(triisopropylsilanyl-oxy-ethynyl)pyrrolidine-1-carboxylic acid isopropyl ester (25). A 2.2 M solution of *n*-BuLi in hexanes (0.83 mL, 1.8 mmol) was added to a solution of 2,2,6,6-tetramethyl-piperidine (0.34 mL, 2.0 mmol) in THF (3.4 mL) at 0 °C. The resulting light yellow solution was stirred at 0 °C for 5 min, then transferred dropwise via cannula to a solution of **18** (201 mg, 0.746 mmol) and dibromomethane (0.13 mL, 1.9 mmol) in THF (3.3 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 3 h, whereupon 10% citric acid (1 mL) was added. The reaction was immediately poured into H_2O (15 mL) and Et_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a crude yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/hexanes (1:3) to afford 220 mg (72%) of **24** as an unstable pale-yellow oil. A portion of the product was immediately dissolved in THF under Ar to avoid decomposition and used in the next reaction.

A solution of 2.2 M *n*-BuLi in hexanes (136 μL, 0.294 mmol) was added to solution of 1,1,1,3,3,3-hexamethyldisilazane (68 μL, 0.321 mmol) in THF (1.6 mL) at 0 °C. The resulting yellow LiHMDS solution was stirred for 10 min at 0 °C, and then transferred via cannula to a solution of **24** (110 mg, 0.268 mmol) in THF (1.4 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 10 min, whereupon a solution of 1.6 M *t*-BuLi in pentane (0.36 mL, 0.56 mmol) was added. The resulting yellow solution was stirred at −78 °C for 1 h, and then freshly distilled TIPSOTf (0.16 mL, 0.59 mmol) was added. After stirring for an additional 10 min, the reaction mixture was diluted with pentane (5 mL) and quenched with saturated $NaHCO_3$ (1 mL) at −78 °C. After warming to ambient temperature, the reaction mixture was poured into H_2O (15 mL) and Et_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3×15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:6) to afford 26 mg (24%) of **25** as a pale-yellow oil. ^{1}H NMR (500 MHz, PhMe-d_8, 100 °C) δ 5.87–5.79 (m, 1H), 5.05–4.89 (comp, 3H), 4.68–4.66 (m, 1H), 3.80–3.78 (m, 1H), 2.19–2.01 (comp, 2H), 1.79–1.60 (comp, 4H), 1.37–1.25 (comp, 2H), 1.22–1.05 (comp, 27H); ^{13}C NMR (125 MHz, PhMe-d_8, 100 °C) δ 154.5, 139.2, 114.4, 89.2, 68.0, 58.4, 49.4, 35.5, 34.0, 33.7, 30.9, 30.8, 22.5, 20.9, 20.7, 20.6, 20.4, 20.2, 20.1, 19.9, 18.1, 17.7, 12.6; IR (neat) 3058, 2944, 2865, 2262, 1688, 1262, 739 cm^{-1}; mass spectrum (CI) *m*/*z* 408.2935 [$C_{23}H_{41}NO_3Si$ (M+1) requires 408.2934], 408 (base), 366, 279.

4.1.16. 2-(1-Triisopropylsilanyloxyvinyl)-9-azabicyclo-[4.2.1]non-2-ene-9-carboxylic acid isopropyl ester (26). A screw-capped vial containing **25** (20 mg, 0.049 mmol) and **11** (8 mg, 10 μmol) in PhMe was sparged with ethylene for 10 min. The vial was then heated with stirring under an atmosphere of ethylene (balloon) at 70 °C for 5 h. The mixture was cooled to room temperature, and then DMSO (1 mL) was added. The solution was stirred for 16 h at room temperature, and then concentrated under reduced pressure. The remaining residue was purified by flash chromatography (neutral Al_2O_3) eluting with Et_2O/pentane (1:3) to afford 11 mg (55%) of **26** as a pale-yellow oil. ^{1}H NMR (500 MHz, PhMe-d_8, 2 rotamers) δ 6.37–6.29 (dt, *J*=16.3, 6.0 Hz, 1H), 5.16–5.15 (d, *J*=8.0 Hz, 0.3H), 5.08–4.98 (m, 1H), 4.90–4.88 (d, *J*=7.6 Hz, 0.7H), 4.66 (s, 0.3H),

4.52–4.46 (comp, 1.3H), 4.36 (s, 0.3H), 4.27–4.22 (comp, 1.2H), 2.27–2.12 (comp, 1.3H), 2.11–1.69 (comp, 4H), 1.69–1.62 (m, 1H), 1.42–1.04 (comp, 29H); ^{13}C NMR (125 MHz, PhMe-d_8) δ 156.9, 153.5, 144.2, 127.2, 126.4, 91.0, 89.8, 67.8, 67.5, 57.3, 56.4, 55.7, 55.1, 34.0, 32.5, 32.3, 31.3, 31.1, 29.8, 23.8, 23.6, 22.4, 22.3, 18.4, 13.3; mass spectrum (CI) *m/z* 408.2933 [$C_{23}H_{41}NO_3Si$ (M+1) requires 408.2934], 448, 436, 408 (base), 394, 364, 348, 322.

4.1.17. (2*R*)-Benzyloxycarbonylamino-5-oxonon-8-enoic acid methyl ester (17c). 4-Bromo-1-butene (1.0 mL, 9.9 mmol) was added to a stirred mixture of magnesium turnings (3.8 g, 160 mmol) in THF (160 mL) at room temperature. The mixture was stirred for 20 min, and an additional portion of 4-bromo-1-butene (7.0 mL, 69 mmol) was added. The resulting mixture was stirred for an additional 30 min, and transferred via cannula to a flask containing TMEDA (24 mL, 160 mmol). The initially cloudy suspension was stirred until all precipitate had disappeared (5 min), whereupon the solution was transferred via cannula to a solution of **16c** (14.6 g, 52.7 mmol) in THF (260 mL) at −78 °C. The mixture was stirred for 1.5 h at −78 °C, and *i*-PrOH (35 mL) was added, and the reaction mixture was warmed to room temperature before pouring into a mixture of 10% H_3PO_4 (300 mL) and Et_2O (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2×100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (2:1) to provide 11.9 g (73%) of **17c** as a pale-yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.69 (br d, J=7.9 Hz, 0.9H), 7.38–7.24 (comp, 5H), 5.76 (ddt, J=16.8, 10.3, 6.5 Hz, 1H), 5.02 (s, 2H), 4.97 (app dq, J=17.2, 1.8 Hz, 1H), 4.94–4.90 (m, 1H), 4.01 (m, 1H), 3.62 (s, 2.6H), 3.55 (s, 0.4H), 2.56–2.43 (comp, 4H), 2.20–2.15 (comp, 2H), 1.95–1.88 (m, 1H), 1.76–1.68 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 208.7, 172.5, 156.0, 137.5, 136.9, 128.3, 127.8, 127.7, 115.0, 65.5, 53.1, 51.8, 40.8, 37.9, 27.2, 24.7; IR (neat) 3342, 2954, 2258, 1712, 1518, 1050, 913, 736 cm^{-1}; mass spectrum (CI) *m/z* 334.1642 [$C_{18}H_{24}NO_5$ (M+1) requires 334.1655], 334, 316, 290 (base), 272, 182, 119.

4.1.18. (2*R*,5*R*)-But-3-enylpyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (27). $BF_3{\cdot}OEt_2$ (15.2 mL, 120 mmol) was added to a solution of Ph_3SiH (15.7 g, 60.1 mmol) in CH_2Cl_2 (40 mL) at room temperature. The solution was stirred for 10 min, and then added via cannula to a stirred solution of **17c** (10.0 g, 30.0 mmol) in CH_2Cl_2 (100 mL) at −78 °C. The reaction mixture was kept with stirring at −78 °C for 0.5 h, whereupon the cooling-bath was removed and stirring was continued at room temperature for an additional 2 h. The reaction mixture was then recooled to −78 °C and poured into a solution of sat. aqueous $NaHCO_3$ (350 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×75 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale-yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:1) to provide 9.37 g (98%) of **27** (*dr*=11:1, by ^{1}H NMR) as a clear oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.38–7.27 (comp, 5H), 5.81 (ddt, J=16.9, 10.3, 6.5 Hz, 1H), 5.15–4.98 (comp, 3H), 4.94–4.91 (m, 1H), 4.36–4.33 (m, 1H), 3.93–3.87 (m, 1H), 3.61 (s, 2.75H, major diast.), 3.57 (s, 0.25H, minor diast.), 2.24–2.17 (m, 1H), 2.14–1.86 (comp, 5H), 1.74–1.66 (m, 1H), 1.56–1.47 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 172.2, 153.4, 137.8, 136.3, 127.6, 127.1, 126.7, 113.8, 65.6, 59.1, 57.8, 51.0, 32.6, 29.2, 28.8, 27.6; IR (neat) 2954, 1752, 1707, 1410, 1204, 1176, 1107, 1005, 913, 748, 696 cm^{-1}; mass spectrum (CI) *m/z* 318.1695 [$C_{18}H_{24}NO_4$ (M+1) requires 318.1705], 318 (base), 274, 182.

4.1.19. (2*R*,5*R*)-But-3-enyl-2-ethynylpyrrolidine-1-carboxylic acid benzyl ester (28). A solution of 1.0 M DIBAL-H in PhMe (7.4 mL) was added to a solution of **27** (1.4 g, 4.4 mmol) in PhMe (22 mL) at −78 °C. The resulting solution was stirred at −78 °C for 3 h, whereupon *i*-PrOH (22 mL) was slowly added via cannula. The cooling bath was removed, and the reaction mixture was warmed to room temperature. To the resulting cloudy-white solution was added solid Cs_2CO_3 (8.6 g, 26 mmol) in one portion. After approximately 1 min, a solution of **9** (1.7 g, 8.8 mmol) in *i*-PrOH (13 mL) was added via cannula. The resulting yellow solution was stirred at room temperature for 17 h, whereupon a mixture of sat. aqueous Rochelle's salt solution (50 mL) and EtOAc (30 mL) were added. The reaction mixture was vigorously stirred for 2 h, and then poured into H_2O (50 mL). The resulting layers were separated, and the aqueous layer was extracted with Et_2O (3×30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to provide 826 mg (67%) of **28** as a pale-yellow oil, and 74 mg (6%) of the corresponding *trans*-product. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.40–7.27 (comp, 5H,), 5.80 (ddt, J=17.0, 10.2, 6.5 Hz, 1H), 5.11 (s, 2H), 5.01 (app dq, J=17.2, 1.7 Hz, 1H), 4.95–4.91 (m, 1H), 4.58–4.55 (m, 1H), 3.88–3.81 (m, 1H), 2.95 (app d, J=2.2 Hz, 1H), 2.17–1.87 (comp, 6H), 1.82–1.75 (m, 1H), 1.60–1.51 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 153.3, 137.6, 136.5, 127.7, 127.0, 126.7, 113.9, 84.5, 71.6, 65.6, 57.4, 48.0, 33.2, 31.2, 28.9; IR (neat) 3307, 2955, 2355, 2250, 1696, 1408, 1355, 1185, 1102 cm^{-1}; mass spectrum (CI) *m/z* 284.1639 [$C_{18}H_{22}NO_2$ (M+1) requires 284.1651], 284 (base), 240.

4.1.20. (2*R*)-But-3-enyl-(5*R*)-2-(1-methylsiletan-1-ylethynyl)pyrrolidine-1-carboxylic acid benzyl ester (29). A solution of **28** (302 mg, 1.07 mmol) in THF (11 mL) was added via cannula to a solution of KHMDS (4.3 mL, 2.1 mmol, 0.5 M in PhMe) in THF (4.3 mL) at −78 °C. The mixture was stirred at −78 °C for 10 min, and then 1-chloro-1-methylsilacyclobutane (0.52 mL, 514 mg, 4.3 mmol) was added via syringe. Stirring was continued at −78 °C for 5 h, whereupon the reaction was poured into a mixture of 1 N HCl (40 mL) and Et_2O (10 mL). The resulting layers were separated, and the aqueous phase was extracted with Et_2O (2×15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a crude oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:3) to afford 309 mg (79%) of **29** as a colorless oil along with 15% recovered **28**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.25 (comp, 5H), 5.80 (br s, 1H), 5.27–4.88 (comp,

4H), 4.64 (br s, 1H), 3.96–3.80 (m, 1H), 2.18–1.80 (comp, 9H), 1.68–1.56 (m, 1H), 1.24–1.10 (comp, 2H), 1.07–0.96 (comp, 2H), 0.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 138.2, 136.9, 128.4, 127.8, 127.7, 127.5, 114.6, 85.1, 76.1, 66.8, 58.3, 49.4, 32.3, 30.3, 30.1, 29.7, 18.3, 15.3, −0.2.; IR(neat) 3067, 3034, 2931, 2711, 1705, 1641, 1496, 1449, 1406, 1355, 1308, 1252, 1184, 1107, 996, 911, 872 cm^{-1}; mass spectrum (CI) *m/z* 368.2053 [$C_{22}H_{30}NOSi$ (M+1) requires 368.2046], 368 (base), 324, 284.

4.1.21. (2*R*)-But-3-enyl-(5*R*)-prop-1-ynylpyrrolidine-1-carboxylic acid benzyl ester (32). A solution of **28** (765 mg, 2.69 mmol) in THF (13 mL) was added to a solution of 1.0 M NaHMDS in THF (8.0 mL, 8.0 mmol) at −78 °C. The resulting solution was stirred for 5 min at −78 °C, and then MeOTf (1.53 mL, 13.5 mmol) was added. After stirring for 2 h at −78 °C, the reaction mixture was poured into a mixture of sat. aqueous $NaHCO_3$ (90 mL) and Et_2O (20 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (3×50 mL) and the combined organic extracts were washed with 1 N HCl (2×70 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a pale-yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to afford 781 mg (97%) of **32** as a pale-yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.39–7.33 (comp, 4H), 7.32–7.27 (m, 1H), 5.80 (ddt, *J*=16.9, 10.2, 6.5 Hz, 1H), 5.10 (dd, *J*=24.0, 12.9 Hz, 1H), 5.03–4.98 (m, 1H), 4.94–4.90 (m, 1H), 4.55–4.51 (m, 1H), 3.85–3.79 (m, 1H), 2.15–1.96 (comp, 4H), 1.95–1.84 (comp, 2H), 1.82–1.72 (comp, 4H), 1.58–1.51 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 153.3, 137.7, 136.6, 127.6, 127.0, 126.7, 113.8, 79.8, 77.2, 65.4, 57.3, 48.3, 33.3, 31.5, 29.0, 28.9, 2.3; IR (neat) 2955, 1702, 1402, 1343, 1208, 1097 cm^{-1}; mass spectrum (CI) *m/z* 298.1800 [$C_{19}H_{24}NO_2$ (M+1) requires 298.1807], 298 (base).

4.1.22. (+)-(1*R*)-2-Isopropenyl-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (33). To a degassed solution of **32** (212 mg, 0.250 mmol) in CH_2Cl_2 (500 mL) was added a solution **11** (744 mg, 2.50 mmol) in degassed CH_2Cl_2 (30 mL). The mixture was stirred under a blanket of argon for 16 h, and then DMSO (0.89 mL) was added to decompose the catalyst. The mixture was stirred for an additional 23 h, whereupon the solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to afford 623 mg (84%) of **33** as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.36–7.25 (comp, 5H), 5.74–5.71 (m, 1H), 5.10–4.96 (comp, 3H), 4.91–4.84 (comp, 2H), 4.39–4.34 (m, 1H), 2.29–2.16 (comp, 3H), 2.13–1.97 (comp, 2H), 1.82 (s, 3H), 1.77–1.68 (comp, 2H), 1.64–1.57 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 152.3, 146.3, 142.4, 136.8, 127.6, 127.0, 126.7, 125.2, 110.5, 65.2, 56.5, 54.7, 31.8, 30.6, 29.2, 22.7, 20.7; IR (neat) 2931, 1701, 1421, 1330, 1107, 1005 cm^{-1}; mass spectrum (CI) *m/z* 298.1799 [$C_{19}H_{24}NO_2$ (M+1) requires 298.1807], 298 (base), 254.

4.1.23. (+)-(1*R*)-2-(1,2-Dihydroxy-1-methylethyl)-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (34). Et_3N (74 μL, 0.53 mmol) was added to a solution of OsO_4 (108 mg, 0.424 mmol) in THF (2.1 mL) at room temperature. The resulting brown solution was stirred for 5 min and then cooled to −78 °C. To this mixture was added a solution **33** (87 mg, 0.29 mmol) in THF (2 mL). The resulting mixture was allowed to warm slowly to room temperature over 2 h, and stirring was continued for 20 h at room temperature. A solution of sat. aqueous $NaHSO_3$ (5 mL) was added, and the mixture was heated to reflux for 2.5 h. The resulting black mixture was cooled to room temperature, diluted with EtOAc (10 mL), and then filtered through a plug of SiO_2, eluting with EtOAc. The filtrate was concentrated under reduced pressure to provide a crude oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (3:1) to afford 89 mg (76%) of **34** as a pale-yellow oil and 15 mg (13%) of the undesired cyclic diol **35** (mp 94–95 °C). ^{1}H NMR (**34**) (500 MHz, DMSO-d_6, 100 °C) δ 7.36–7.27 (comp, 5H), 5.64–5.61 (m, 1H), 5.06 (app q, *J*=12.6 Hz, 2H), 4.68–4.66 (m, 1H), 4.41–4.37 (m, 1H), 4.02–3.93 (comp, 2H), 3.39–3.25 (comp, 2H), 2.28–2.12 (comp, 3H), 2.03–1.95 (m, 1H), 1.86–1.80 (comp, 2H), 1.73–1.67 (m, 1H), 1.61–1.55 (m, 1H), 1.26–1.15 (comp, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 151.4, 136.7, 127.7, 127.1, 127.0, 122.1, 73.9, 68.0, 65.3, 55.5, 54.9, 31.1, 28.0, 24.2, 22.6; IR (neat) 3401, 2931, 1672, 1426, 1326, 1114, 914, 732 cm^{-1}; mass spectrum (CI) *m/z* 332.1854 [$C_{19}H_{26}NO_4$ (M+1) requires 332.1862], 332, 314 (base).

4.1.24. (+)-(1*R*)-2-Acetyl-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (36). Solid $NaIO_4$ (140 mg, 0.655 mmol) was added to a solution of **34** (70 mg, 0.21 mmol) in 50% aqueous THF (4 mL) at room temperature. The reaction mixture was stirred for 1.5 h, and then diluted with H_2O (2 mL). The solution was poured into a mixture of H_2O (15 mL) and Et_2O (5 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (3×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale-yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (8:1) to afford 60 mg (95%) of **36** as a pale-yellow oil. All data in accordance with the literature.[44] $[\alpha]_D^{26}$ −36.1 (*c* 1.42, CH_3OH) (lit.[44] $[\alpha]_D^{22}$ −37.5 (*c* 1.12, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.22 (comp, 5H), 6.83–6.75 (m, 1H), 5.27 (d, *J*=8.9 Hz, 1H), 5.16–4.98 (comp, 2H), 4.52–4.38 (m, 1H), 2.47–2.00 (comp, 8H), 1.74–1.61 (comp, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 153.4, 149.3, 142.3, 136.8, 128.4, 127.9, 127.7, 66.3, 56.0, 53.0, 31.6, 30.4, 28.5, 25.3, 24.1; IR (neat) 3538, 2951, 1700, 1665, 1418, 1106 cm^{-1}; mass spectrum (CI) *m/z* 300.1587 [$C_{18}H_{22}NO_3$ (M+1) requires 300.1600], 300 (base), 256, 192.

4.1.25. (+)-(1*R*)-2-Acetyl-9-azabicyclo[4.2.1]-2-nonene (1). Freshly distilled TMSI (122 μL, 0.856 mmol) was added to a solution of **36** (122 mg, 0.408 mmol) in MeCN (1.4 mL) at −10 °C. The resulting solution was stirred for 20 min in the absence of light. A solution of 1.25 M methanolic HCl (1 mL) was added and the resulting solution was maintained in the dark while warming to room temperature. The solution was concentrated under reduced pressure, and the resulting solid was dissolved in H_2O (10 mL). The aqueous solution was extracted with CH_2Cl_2 (2×4 mL). The aqueous phase was then basified to pH=12

with NH_4OH and extracted first with CH_2Cl_2 (2×4 mL) and then with 3:1 CH_2Cl_2/*i*-PrOH (2×5 mL). The combined organics were rapidly dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale-yellow oil. The light sensitive free-base was dried at 0.1 mm Hg for 1 h to afford 67 mg (99%) of **1** as a pale-yellow oil. The ^1H and ^{13}C NMR data were consistent with those reported in the literature.[44,46] ^1H NMR (400 MHz, $CDCl_3$) δ 6.89–6.84 (m, 1H), 4.66 (app d, J=8.9 Hz, 1H), 3.82–3.75 (m, 1H), 3.13 (br s, 1H), 2.52–2.34 (comp, 2H), 2.25 (s, 3H), 2.21–2.09 (m, 1H), 2.01–1.92 (m, 1H), 1.82–1.57 (comp, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 152.4, 143.6, 58.1, 54.3, 33.5, 33.1, 30.5, 25.8, 25.2; IR (neat) 3392, 2933, 1663, 1433, 1397, 1361, 1258, 1228, 847 cm^{-1}; mass spectrum (CI) *m/z* 166.1234 [$C_{10}H_{16}NO$ (M+1) requires 166.1232], 166 (base), 149.

4.1.26. (+)-(1*R*)-2-Acetyl-9-azabicyclo[4.2.1]-2-nonene hydrochloride (1·HCl). A solution of 1.25 M HCl in MeOH (1 mL) was added to a solution of **1** (48 mg, 0.16 mmol) in dry MeOH (1 mL) at 0 °C. The solvent was removed under reduced pressure, and the crude oil was dried under vacuum (0.3 mm Hg) for 15 h. The resulting off-white foam was azeotropically dried with PhH (2×0.3 mL) and then under vacuum (0.3 mm Hg) for 2 h. The resulting foam was dissolved in a solution of 6% MeOH/Et_2O (2 mL), at 50 °C. The solution was cooled to room temperature and placed in a 4 °C refrigerator for 5 d. The resulting colorless prisms were collected by vacuum filtration, rinsing with cold Et_2O (5 mL), and dried at 0.3 mm Hg for 2 d to afford 32 mg (100%) of **1·HCl**. All spectra in accordance with the literature.[46] $[\alpha]_D^{27}$ +37.3 (*c* 2.08, abs. EtOH) [(lit.[46] $[\alpha]_D^{24}$ +43.2 (*c* 0.676, abs. EtOH), (lit.[54] $[\alpha]_D^{24}$ +36 (*c* 0.85, EtOH)]; mp 151–153 °C (lit.[46] mp 152–153 °C). ^1H NMR (500 MHz, $CDCl_3$) δ 10.02 (br s, 1H), 9.42 (br s,), 7.11 (dd, J=8.2, 3.4 Hz, 1H), 5.23–5.19 (m, 1H), 4.37–4.29 (m, 1H), 2.65–2.58 (m, 1H), 2.56–2.47 (comp, 2H), 2.42–2.30 (comp, 5H), 1.94–1.78 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 145.4, 143.9, 58.3, 52.1, 30.2, 27.7, 27.5, 25.2, 23.6; IR (neat) 3417, 2924, 1661, 1471, 1432, 1403, 1364, 1269, 1230, 911, 743 cm^{-1}; mass spectrum (CI) *m/z* 200.0835 [$C_{10}H_{15}NOCl$ (M−1) requires 200.0842], 216, 202, 200 (base), 179.

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