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Synthesis of the Stenine Ring System from Pyrrole

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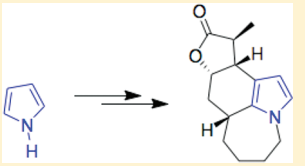
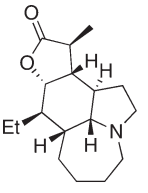
Supporting Information

ABSTRACT: The skeleton of the stemona alkaloid, stenine, has been synthesized starting from pyrrole, employing an asymmetric organocatalyzed cyclization, Sonogashira coupling, a diastereoselective intramolecular propargylic Barbier reaction, cyclocarbonylation, and diastereoselective alkene reduction. Modulation of the electron-rich nature of the pyrrole nucleus by employing an α-trifluoroacetyl group is essential. The α-trifluoroacetyl group may be rapidly removed under carefully defined, mild conditions.



INTRODUCTION

Pyrrole is a promising starting material for the synthesis of complex pyrrolidines as substitution can be directed to the N-, α-, and β-positions by the judicious choice of conditions and use of temporary substituents,[1−6] allowing the rapid buildup of molecular complexity from simple starting materials. Historically,[7] overcoming the natural tendency for electrophilic attack α has been a challenge, but β-substitution may be achieved by the use of bulky N-substituents,[8−10] or strongly electron-withdrawing α′-substituents.[11] Nevertheless, using pyrroles in natural product synthesis is challenging. While the highly electron-rich nature of the pyrrole ring can promote certain productive reactions, it can also generate significant challenges by promoting decomposition pathways and destabilizing functional groups. This effect extends to substituents conjugated to the pyrrole ring. Thus, to employ the pyrrole ring as a starting material, it is necessary to have strategies to moderate these properties. An electron-withdrawing group in the α-position should be able to achieve this as well as direct electrophilic attack, but efficient and mild methods for the late-stage removal of the electron-withdrawing group are required. The stemona alkaloids contain a pyrrolidine, dihydropyrrole, or pyrrole ring embedded within a complex polycyclic framework.[12−14] Despite modest biological activity, they have attracted the attention of synthetic organic chemists due to the structural and stereochemical challenges presented. In addition to the N-heterocycle, the stemona alkaloids frequently possess an α-methyl butyrolactone moiety. We recently employed a combination of a highly diastereoselective intramolecular propargylic Barbier reaction and ruthenium-catalyzed cyclocarbonylation to synthesize the butenolide natural product, mintlactone,[15] and the stemona alkaloid, stemoamide.[16] We now wish to report a synthesis of the ring system of stenine **1**, starting from pyrrole and utilizing an intramolecular propargylic Barbier reaction to install the lactone. The challenges arising from the use of pyrrole, outlined above, are addressed. Stenine has been the subject of a number of syntheses[17−24] and related studies.[25−28] Our specific target was tetracyclic pyrrole **2**, excluding the ethyl substituent of stenine at this stage. The same tetracyclic core is shared with other stemona alkaloids, such as tuberostemonine and its dehydro analogues.



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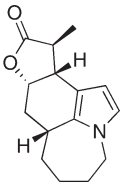

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RESULTS AND DISCUSSION

To form the azepine ring, we planned to use the asymmetric Friedel−Crafts/Michael cyclization reported by Banwell,[29] employing MacMillan's catalyst (Scheme 1). To this end, pyrrole was cleanly N-alkylated according to the method of Heaney and Ley.[30] Cross-metathesis of N-alkylated pyrrole **4** with crotonaldehyde was then carried out. This reaction proceeded in excellent yield even with catalyst loadings as low as 0.5 mol %. The aldehyde **5** must be purified with great care because the subsequent cyclization is also catalyzed by silica gel to give the racemic azepine (±)-**6**, which coelutes with the starting aldehyde during chromatography. Chromatography on silica gel doped with triethylamine prevents this premature cyclization. With the chemically pure aldehyde **5** in hand, cyclization with MacMillan's catalyst gave the labile azepine aldehyde **6**, which was reduced with sodium borohydride to the corresponding alcohol **7** before isolation.[31] The ee of the alcohol, determined by chiral HPLC, was found to be 95%.

With the N- and α-substituents installed, an electron-withdrawing group at the α′-position was required to provide chemical access to the β-carbon (Scheme 2). Both the trichloroacetyl and the trifluoroacetyl derivatives **8a,b** were prepared by

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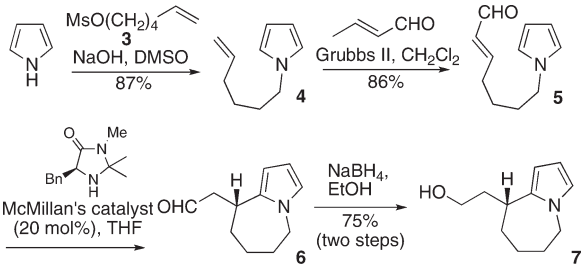
treatment of pyrrole **7** with either the acid chloride[11] or the anhydride,[32] respectively. In each case, the free alcohol group was also acylated. In the ^{1}H NMR spectra of each of these compounds, the signals for the methylene protons α to nitrogen showed extensive line broadening at room temperature. Variable-temperature (VT) NMR studies were carried out using **8b**, and the signals were clearly resolved at −50 °C. Some line broadening was also observed in the ^{13}C spectra. No such effect was observed after iodination (compounds **9a,b**), but the effect reappeared to a lesser extent after Sonogashira coupling (see below). Clean β-iodination was then achieved by treatment with iodine monochloride. The rate of iodination is highly solvent-dependent: at 0 °C, iodination of trifluoromethyl ketone **8a** in dichloromethane is complete within 2 h. In diethyl ether, 48 h is required. We attribute this to the formation of a less reactive solvent−pseudohalogen complex with ether.[33] As the acylation reaction is a very clean reaction, it can be combined with iodination in a one-pot process. The yield of acylation is, however, significantly higher in diethyl ether. The optimum method, therefore, requires a solvent switch between the two reactions. The trichloroacetyl derivative **9b** could be converted to the methyl ester **10b** cleanly, following the procedure of Belanger.[11,34] The trichloroester was concomitantly cleaved in this process. In the case of the trifluoromethyl ketone **9a**, the trifluoroacetate group was cleaved easily, a reaction conveniently carried out using polyvinylpyridine (PVP) as the base catalyst.

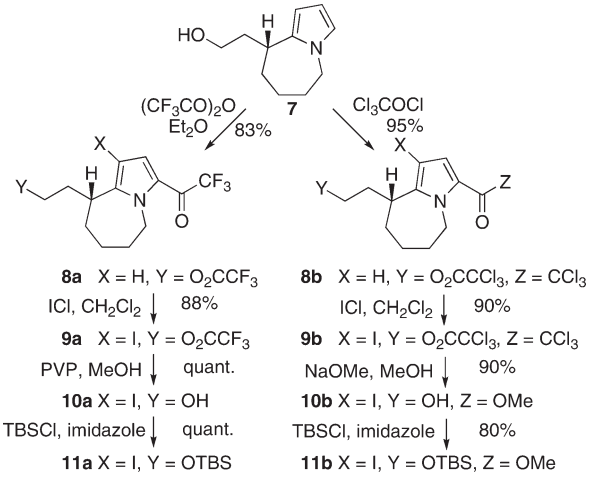
With the iodides **10a,b** in hand, the free alcohols were reprotected as their TBS ethers **11a,b**. This protecting group switch was necessary as submitting either of the trihaloesters **9a,b** to the Sonogashira reaction with propargyl alcohol resulted in deacylation but not the desired coupling.

Although Sonogashira coupling of the TBS ether **11a** of the trifluoromethyl ketone with propargyl alcohol proceeded in 70% yield under the usual homogeneous conditions,[35,36] the best results, 87% yield of alkyne **12a**, were obtained under Cosford conditions using palladium on carbon (Scheme 3).[37] In contrast, Sonogashira coupling of the methyl ester **11b** was more challenging. At room temperature in THF, the reaction was very slow, giving a 14% yield of alkyne **12b** after 18 h. Only a modest improvement was observed at a substantially higher temperature: 44% yield after 18 h at 65 °C. An acceptable yield was only obtained when the solvent was changed to DMSO: 60% yield after 28 h at 50 °C. The difference between the two seemingly similar substrates appears to lie in the electronic nature of the

Scheme 1. Pyrroloazepine Synthesis



Scheme 2. Trisubstituted Pyrrole Synthesis



Scheme 3. Sonogashira and Barbier Reactions

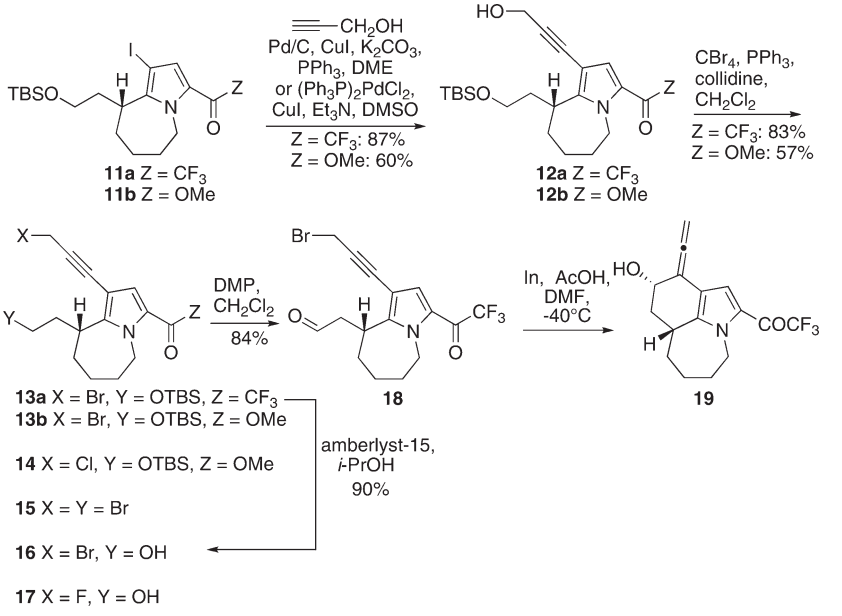


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Table 1. Conversion of Alcohol 12a to Bromide 13a

entry	reagents[a]	yield of bromide **13a** (%)	yield of dibromide **15** (%)
1	CBr_4, PPh_3	41	10
2	CBr_4, PPh_3, $CaCO_3$	60	5
3	CBr_4, PPh_3, Et_3N	0	0
4	CBr_4, PPh_3, collidine	83	0

[a] All reactions were carried out in CH_2Cl_2 for 1 h at 0 °C in the presence of molecular sieves.

Table 2. Deprotection of Silyl Ether 13a

entry	catalyst or reagent	solvent	time/h	temp	yield (%)
1	Amberlyst-15	MeOH	14	rt	0
2	Amberlyst-15	MeOH	2	rt	10[a]
3	PPTS	MeOH	10	rt	0
4	TBAF	THF	14	rt	48[b]
5	Amberlyst-15	CH_2Cl_2, MeOH (1:10)	24	rt	60
6	Amberlyst-15	*i*-PrOH[c]	48	rt	70
7	Amberlyst-15	*i*-PrOH	12	60 °C	60
8	Amberlyst-15	*i*-PrOH[d]	24	rt	90

[a] 20% of starting material recovered. [b] No bromide obtained, yield of the corresponding propargylic fluoride **17**. [c] Technical grade. [d] Anhydrous.

pyrrole ring. It is known that Sonogashira coupling is faster with more electron-poor aryl halides,[38] and therefore, we believe that the more electron-withdrawing trifluoroacetyl group is critical. To set the stage for the intramolecular propargylic Barbier reaction, it was then necessary to convert the propargylic alcohol to the corresponding bromide. This seemingly trivial transformation was rendered troublesome (table 1) by the pyrrole, which, despite the electron-withdrawing methoxycarbonyl or trifluoroacetyl group, remains electron-rich. Attempts to form the bromide **13b** of the methyl ester using the method that we employed previously (MsCl, Et_3N, then LiBr in THF)[15,16] failed due to decomposition. Indeed, it proved to be impossible to isolate the mesylate, although we were able to isolate the corresponding chloride **14** in a mere 10% yield. Under Appel conditions[39,40] (Table 1) with the addition of molecular sieves, a modest yield of the bromide **13a** was obtained,[41] accompanied by a small amount of the dibromide **15** (entry 1).[42] The isolation of this byproduct indicated to us the formation of HBr from adventitious moisture. Buffering the reaction mixture with calcium carbonate resulted in an increased yield of the desired bromide **13a** and a reduced yield of the dibromide **15** (entry 2). Use of a weak homogeneous base with low nucleophilicity, collidine, resulted in formation of the desired bromide **13a** in 83% yield (entry 4). Addition of Et_3N, on the other hand, resulted in no isolable bromide (entry 3). Similarly, the methyl ester **12b** could be converted to the bromide **13b** under Appel conditions with added molecular sieves and collidine but in only 57% yield. This, again, shows the superiority of the more electron-withdrawing trifluoroacetyl group over the methoxycarbonyl group.

A second seemingly trivial transformation, removal of the silyl protecting group, was also troublesome (Table 2), again due to the electron-rich nature of the pyrrole. Attempted deprotection of trifluoromethyl ketone **13a** under the conditions that we habitually use, Amberlyst-15 in methanol,[43−45] gave only a trace

Table 3. Intramolecular Propargylic Barbier Reaction

entry	reagents and solvent	time/h	temp	yield (%)[a]	dr
1	Zn, NH_4Cl, THF	5	rt	40	1:1
2	Zn, AcOH, DMF (1:1)	4	rt	15	1:1
3	$SnCl_2$, NaI, DMF, H_2O (10:1)	2	rt	80	1.3:1
4	$SnCl_2$, NaI, DMF, H_2O (10:1)	12	−10 °C	70	2:1
6	In, DMF	12	rt	0	
7	In, AcOH	2	rt	70	2.85:1
8	In, AcOH (10 equiv), THF	4	rt	60	2.85:1
9	In, AcOH (10 equiv), THF	20	−40 °C	40	3.6:1
10	In, AcOH (10 equiv), toluene	18	rt	50	2:1
11	In, AcOH (10 equiv), DMSO, H_2O	2	rt	73	2:1
12	In, AcOH (10 equiv), DMF, H_2O	4	rt	75	2:1
13	In, AcOH, DMF (1:1)	2	rt	78	2.85:1
14	In, AcOH, DMF (1:1)	20	−40 °C	70	3.6:1

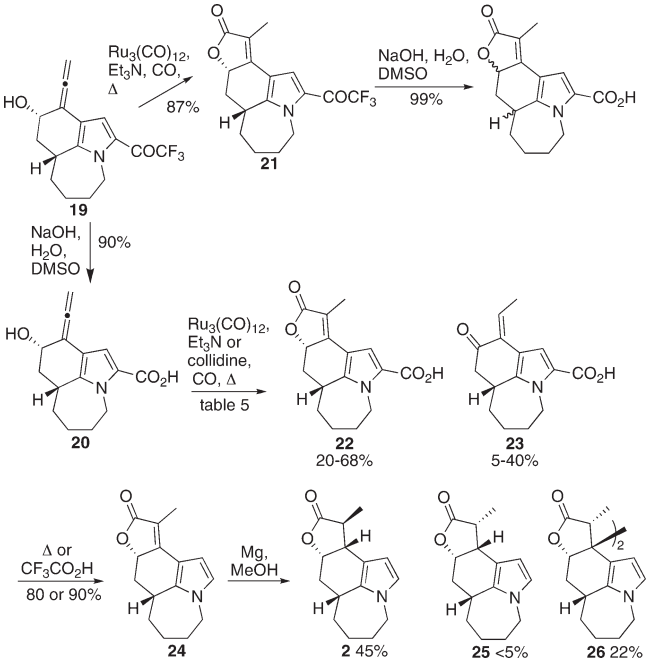
[a] Combined yield of the two diastereoisomers.

of the desired product **16** with a limited reaction time (entry 2). A prolonged reaction time resulted in complete decomposition (entry 1). Attributing this to decomposition through a carbocation pathway, we reduced the polarity of the medium by, first, diluting the methanol with dichloromethane (entry 5) and, subsequently, switching to isopropyl alcohol (entries 6−8). Ultimately, the best result, a 90% yield of alcohol **16**, was obtained using anhydrous isopropyl alcohol. In contrast, even under these conditions, attempted deprotection of the methyl ester **13b** resulted in decomposition. As a consequence, we could not carry any of the methyl ester substituted materials further in the synthesis. Use of TBAF resulted in formation of the propargylic fluoride **17** (entry 4). Oxidation of alcohol **16** to aldehyde **19** was achieved using the Dess−Martin periodinane.[46]

With the aldehyde **18** in hand, the key intramolecular Barbier reaction for formation of the six-membered ring of allene **19** was surveyed (Table 3). Previously, we have employed stannous chloride, zinc, and indium in such transformations.[15,16] No diastereoselectivity was observed using zinc (entries 1 and 2); a slight improvement was found with stannous chloride at a reduced temperature (entries 3 and 4). We, therefore, turned our attention to indium. No reaction was observed using indium in DMF (entry 6), but the allenic alcohol **19** was obtained employing indium in mixtures of acetic acid[47] with organic solvents (entries 7−14). The highest diastereoselectivity and yield were obtained using indium in an acetic acid/DMF mixture at −40 °C (entry 14). Replacing DMF with THF gave, under the same conditions, the same diastereoselectivity but a lower yield (entry 9). The presence of acetic acid is essential to obtaining high reactivity at this low temperature. The major isomer was isolated in pure form in 52% yield by column chromatography, and its stereochemistry was shown to be *cis* by X-ray crystallography.[48]

For the end game, we needed to form and reduce the lactone ring by cyclocarbonylation and remove the trifluoroacetyl group. After substantial experimentation, it was found that the best sequence was to intermingle these processes (Scheme 4). Removal of the trifluoroacetyl group involves hydrolysis of the ketone to a carboxylic acid,[49,50] which may be regarded as a hemihaloform reaction, followed by the thermal decarboxylation of the pyrrole carboxylic acid.[51] Hydrolysis was found to proceed rapidly upon treatment with sodium hydroxide in wet DMSO (Table 4) with the reaction going to completion within minutes

Scheme 4. Cyclocarbonylation, Hydrolysis, Decarboxylation, and Reduction



to give acid **20** in 90% yield (entry 4). Lithium hydroxide is often employed for the rapid hydrolysis of esters. Surprisingly, hydrolysis of the trifluoromethyl ketone with this reagent under otherwise identical conditions required a prolonged reaction time; a shorter reaction time could be realized in pure DMSO, but in both cases, substantial epimerization was observed (entries 2 and 3). We believe that this is at the pyrrolic position as the corresponding carbanion is conjugated through the pyrrole ring with the ketone group. Cesium hydroxide could, however, be employed to achieve rapid hydrolysis without epimerization (entry 5). We postulate that lithium hydroxide remains ion-paired and, hence, less reactive in DMSO.[52−54] With sodium hydroxide and cesium hydroxide, the anion is "naked".

Cyclocarbonylation of trifluoromethyl ketone **19** under Takahashi's conditions,[55−57] $Ru_3(CO)_{12}$ in dioxane under CO pressure with a triethylamine additive, gave the expected butenolide **21** in good yield, but extensive epimerization was observed on attempted cleavage of the trifluoroacetyl group even under our optimized conditions using NaOH in DMSO. The position of epimerization was not apparent from the ^{1}H NMR spectrum. In contrast, cyclocarbonylation of the carboxylic acid **20** under these conditions proceeded to give the butenolide **22** in just 40% yield (Table 5, entries 1). A byproduct, identified as enone **23**, was isolated in 30% yield. Both Takahashi[57] and Hong[58] have proposed mechanisms for the cyclocarbonylation that involve formation of a carbon−ruthenium single bond at the central carbon of the allene.[59] Formation of enone **23** could involve C−H bond formation by reductive elimination from such intermediates. When collidine[60] rather than triethylamine was employed as the additive in the reaction, however, formation of enone **23** was minimized (14%) and butenolide **22** was obtained in 68% yield (entry 4). Heating the neat carboxylic acid **22** at 160 °C resulted in decarboxylation and gave the pyrrole **24** in 80% yield; alternatively, treatment of the carboxylic acid **22** with trifluoroacetic acid in dichloromethane at reflux, gave pyrrole **24** in slightly higher

Table 4. Hydrolysis of Trifluoroacetylpyrrole 19

entry	reagent and solvents	time/h	temp	yield (%)	epimerization
1	LiOH, DMF, H_2O	14	70 °C	dec.	
2	LiOH, DMSO	3	50 °C	80	dr 1:1
3	LiOH, DMSO, H_2O	24	rt	80	dr 4.4:1
4	NaOH, DMSO, H_2O	0.25	rt	90	none
5	CsOH, DMSO, H_2O	1	rt	80	none

Table 5. Cyclocarbonylation of Allenol 21

entry	reagent and solvents	catalyst loading/ mol %	yield of butenolide (%) **22**	yield of enone (%) **23**
1	dioxane, Et_3N (6 equiv)	4	40	30[a]
2	Et_3N (neat)	4	20	40[b]
3	2,4,6-collidine (neat)	4	50	5[c]
4	dioxane, collidine (6 equiv)	4	68	14[c]

[a] A ca. 2:1 mixture of *E*/*Z* isomers. [b] A ca. 10:1 mixture. [c] One isomer.

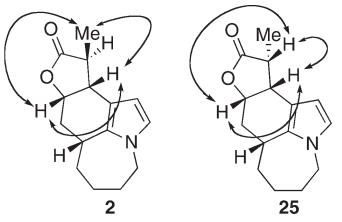


Figure 1. Significant NOE interactions observed during NOESY experiments for lactones **2** and **25**.

yield (90%). In contrast, treatment of the sensitive allenol **20** under the same sets of conditions resulted in decomposition.

Finally, we attempted to reduce the alkene of the butenolide **24**. In our synthesis of stemoamide, we followed the lead of Mori[61,62] and Jacobi[63,64] in employing nickel boride. In the case of butenolide **24**, no reaction was observed with this reagent due, we presume, to conjugation with the pyrrole. Reduction was initially achieved using magnesium, activated with mercuric chloride, in methanol.[65,66] By ^{1}H NMR, a mixture of products was obtained. Two isomers of the desired structure could be obtained by column chromatography. The major isomer **2**, isolated in 35% yield, was determined to have the structure shown by analysis of coupling constants and NOE interactions in the NOESY spectrum (Figure 1). This assignment was later confirmed by X-ray crystallography.[48] The minor isomer **25**, isolated in 12% yield, was shown to be epimeric at the position α to the lactone carbonyl.[67] Employing magnesium powder, which eliminates the need for mercuric chloride, and a prolonged reaction time led to a stereoselective reaction giving lactone **2** in 45% yield accompanied by only a trace of isomer **25**. In all cases, a byproduct was formed, identified as the dimer **26**.[48] This is apparently formed by coupling of pyrrolic radicals or radical anions.

CONCLUSION

Our synthesis of this tetracyclic compound demonstrates the versatility of pyrrole of a starting material for alkaloids by bond

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formation at multiple sites around the heteroaromatic nucleus. The high electron density of the pyrrole ring can complicate many otherwise straightforward reactions but can be controlled by using the trifluoroacetyl group, rapidly and easily removable under our new, mild conditions. The trifluoroacetyl group is much more effective than the methoxycarbonyl group in this regard. This is also a contribution to the synthesis of the stemona alkaloids using an unusual approach.

EXPERIMENTAL SECTION

General Experimental Details. All reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware (120 °C), which was cooled under vacuum. Anhydrous tetrahydrofuran and diethyl ether were distilled from sodium metal and benzophenone under nitrogen. Anhydrous dichloromethane was dried by distillation from CaH_2 immediately prior to use under nitrogen. Anhydrous methanol and isopropyl alcohol were distilled from activated magnesium under nitrogen. All other solvents and reagents were used as received. Analytical TLC was carried out on precoated plates (silica gel 60, F254). Column chromatography was performed with silica gel 60 (230−400 mesh). ^{1}H NMR spectra were recorded at 300, 400, or 500 MHz. ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz. Chemical shifts are recorded in parts per million, and coupling constants J are recorded in Hertz. Melting points are uncorrected. Optical rotations are given with units of 10^{-1} deg cm^2 g^{-1}.

Hex-5-enyl methanesulfonate (3)[68]. Triethylamine (41.7 mL, 300 mmol) and methanesulfonyl chloride (23.1 mL, 300 mmol) were added to an ice cold solution of hex-5-en-1-ol (20 g, 200 mmol) in dichloromethane (200 mL), and the mixture was stirred at the same temperature for 1 h. A saturated aqueous NH_4Cl solution (200 mL) was added, and the mixture was extracted with Et_2O (2 × 300 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure to give mesylate **3** (35.2 g, 99%) as a yellow oil, which was used without purification: FTIR (neat, cm^{-1}) ν_{max} 2939, 1639, 1354, 1175; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84−5.71 (1H, m), 5.08−4.95 (2H, m), 4.23 (2H, t, J = 6.4 Hz), 3.0 (3H, s), 2.10 (2H, app. q, J = 7.1 Hz), 1.81−1.70 (2H, m), 1.56−1.45 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 115.0, 69.9, 37.0, 32.8, 28.2, 24.4.

1-(Hex-5-enyl)-1*H*-pyrrole (4). Pyrrole (13.8 mL, 200 mmol) was added to a suspension of sodium hydroxide (16 g, 400 mmol) in dry DMSO (130 mL) under nitrogen at room temperature. After stirring for 30 min at room temperature, hex-5-enyl methanesulfonate **3** (35.6 g, 200 mmol) was added slowly at 0 °C. The mixture was allowed to warm to room temperature gradually (ice bath was not removed, but allowed to melt). After stirring for 14 h at room temperature, the reaction mixture was poured into ice water (300 mL) and the mixture was extracted with Et_2O (3 × 400 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (300 g, 2% EtOAc/hexane) to give 1-(hex-5-enyl)-1*H*-pyrrole **4** (25.9 g, 87%) as a yellow oil: FTIR (neat, cm^{-1}) ν_{max} 2930, 1640; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (2H, br s), 6.14 (2H, br s), 5.85−5.72 (1H, m), 5.0 (1H, br d, J = 19 Hz), 4.97 (1H, br d, J = 11.4 Hz), 3.88 (2H, t, J = 7.1 Hz), 2.08 (2H, q, J = 7.1 Hz), 1.79 (2H, quint, J = 7.3 Hz), 1.4 (2H, quint, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 120.2 (2C), 114.8, 107.7 (2C), 49.4, 33.2, 30.9, 25.9; MS (ESI+) m/z (%) 150 (M + 1, 100); HRMS calcd for $C_{10}H_{16}N$ (M^+ + H) 150.1283, found 150.1281.

(*E*)-7-(1*H*-Pyrrol-1-yl)hept-2-enal (5). To a solution of 1-(hex-5-enyl)-1*H*-pyrrole **4** (20 g, 134.2 mmol) in dry dichloromethane (200 mL) was added crotonaldehyde (55.3 mL, 671.1 mmol), followed by Grubbs II catalyst (569 mg, 0.671 mmol) under an inert atmosphere. The reaction mixture was heated at reflux for 56 h. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on basified silica gel (300 g, 15 mL of Et_3N) eluting with 5% EtOAc/hexane to give (*E*)-7-(1*H*-pyrrol-1-yl)hept-2-enal **5** (20.35 g, 86%) as a yellow oil: FTIR (neat, cm^{-1}) ν_{max} 2933, 1683, 1637, 1500; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (1H, d, J = 7.8 Hz), 6.80 (1H, dt, J = 15.6, 6.8 Hz), 6.65 (2H, d, J = 2.0 Hz), 6.15 (2H, d, J = 2.0 Hz), 6.10 (1H, ddt, J = 15.6, 7.8, and 1.4 Hz), 3.91 (2H, t, J = 6.9 Hz), 2.4−2.28 (2H, m), 1.82 (2H, quint, J = 7.0 Hz), 1.52 (2H, quint, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 157.5, 133.0, 120.2 (2C), 107.9 (2C), 49.0, 31.9, 30.8, 24.8; HRMS calcd for $C_{11}H_{16}NO$ (M^+ + H) 178.1232, found 178.1232.

(*R*)-2-(6,7,8,9-Tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)-acetaldehyde (6): Colorless oil; FTIR (neat, cm^{-1}) ν_{max} 2923, 1719, 1294; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (1H, s), 6.57 (1H, br s), 6.0 (1H, t, J = 3.0 Hz), 5.83 (1H, br s), 4.06 (1H, dd, J = 14.3, 5.7 Hz), 3.94 (1H, dd, J = 14.0, 11.1 Hz), 3.32 (1H, app. q, J = 7.85 Hz), 2.95 (1H, dd, J = 16.7, 6.4 Hz), 2.74−2.65 (1H, m), 2.1−1.12 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 136.3, 121.8, 105.5, 104.9, 49.8, 47.6, 34.4, 32.8, 29.5 (br), 29.3; MS (ESI+) m/z (%) 178 (M^+ + 1, 100); HRMS calcd for $C_{11}H_{16}NO$ (M^+ + H) 178.1232, found 178.1233.

(*R*)-2-(6,7,8,9-Tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)-ethanol (7)[26]. To a solution of (*E*)-7-(1*H*-pyrrol-1-yl)hept-2-enal **5** (10 g, 56.5 mmol) in THF (200 mL) was added (*S*)-MacMillan's catalyst (3.76 g, 11.2 mmol), followed by 6 mL of water at −20 °C. After stirring for 20 h, the reaction mixture was diluted with ethanol (100 mL) and warmed to 0 °C. Sodium borohydride (2.13 g, 56.5 mmol) was added portionwise to the reaction mixture. After stirring for 2 h at room temperature, the reaction mixture was poured slowly into a saturated aqueous solution of NH_4Cl (300 mL) and the mixture was extracted with ethyl acetate (3 × 400 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (300 g, 15% EtOAc/hexane) to give (*R*)-2-(6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)ethanol **7** (7.6 g, 75%) as a colorless oil: FTIR (neat, cm^{-1}) ν_{max} 3361, 2922, 1486, 1078; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (1H, t, J = 2.1 Hz), 5.98 (1H, t, J = 3.0 Hz), 5.88 (1H, t, J = 2.3 Hz), 4.12−3.86 (2H, m), 3.77 (2H, br s), 2.89 (1H, br s), 2.18−2.10 (1H, m), 2.02−1.62 (8H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7 (br), 121.6, 105.6, 105.0 (br), 61.4, 50.0, 36.3 (br), 34.8, 34.1 (br), 29.6, 28.7 (br); MS (ESI+) m/z (%) 180 (M^+ + 1, 100); HRMS calcd for $C_{11}H_{18}NO$ (M^+ + H) 180.1388, found 180.1389; $[\alpha]^{22.4}_D$ = 0.75 (c = 1.75, $CHCl_3$).

(*R*)-2-(3-(2,2,2-Trifluoroacetyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)ethyl 2,2,2-trifluoroacetate (8a). Trifluoroacetic anhydride (9.5 mL, 68.3 mmol) was added to a stirred solution of alcohol **7** (4.89 g, 27.3 mmol) in dry diethyl ether (50 mL) at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (50 mL). The mixture was extracted with diethyl ether (2 × 200 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (150 g, 5% EtOAc/hexane) to give trifluoromethyl ketone **8a** (8.4 g, 83%) as a colorless oil: FTIR (neat, cm^{-1}) ν_{max} 2936, 1785, 1657, 1134; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.13 (1H, m), 6.08 (1H, d, J = 4.4 Hz), 5.37 (1H, br s), 4.55−4.38 (2H, m), 4.11 (1H, br s), 2.95 (1H, app. q, J = 7.8 Hz), 2.43−2.32 (1H, m), 2.14−1.21 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (q, J = 34.4 Hz), 157.3 (q, J = 42.0 Hz), 151.0, 124.2 (2C), 117.2 (q, J = 278 Hz), 114.3 (q, J = 286 Hz), 108.0, 66.0, 46.0, 34.8, 32.4, 31.4, 28.6, 27.6; MS (GC) m/z (%) 371 (M^+, 82), 302 (50), 230 (100); HRMS calcd for $C_{15}H_{16}F_6NO_3$ (M^+ + H) 372.1034, found 372.1037; $[\alpha]^{21.6}_D$ = −79.6 (c = 2, $CHCl_3$).

(*R*)-2-(3-(2,2,2-Trichloroacetyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)ethyl 2,2,2-trichloroacetate (8b). A solution of trichloroacetyl chloride (11.8 mL, 64.7 mmol) in dry diethyl ether (50 mL) was added slowly to a solution of hydroxypyrrole **7** (4.63 g, 25.86 mmol) in dry diethyl ether (100 mL) at 0 °C. After stirring at room temperature for 4 h, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (100 mL). The mixture was extracted with diethyl ether (2 × 300 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure to give trichloroacetate **8b** (11.5 g, 95%) as a gray solid, which was used without purification: mp 78−80 °C; FTIR (neat, cm^{-1}) ν_{max} 2931, 1764, 1661, 1235; ^1H NMR (400 MHz, $CDCl_3$, −50 °C) δ 7.5 (1H, d, J = 4.6 Hz), 6.08 (1H, d, J = 4.1 Hz), 5.59 (1H, dd, J = 14.2, 5.0 Hz), 4.72−4.38 (2H, m), 3.71 (1H, app. t, J = 12.8 Hz), 2.92 (1H, app. q, J = 7.3 Hz), 2.51−2.38 (1H, m), 2.21−1.22 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 161.9, 150.0, 124.1, 121.5, 106.7, 96.8, 89.7, 67.2, 46.2, 34.7, 32.5, 31.6, 28.8, 27.6; HRMS calcd for $C_{15}H_{16}Cl_6NO_3$ (M^+ + H) 467.9261, found 467.9262; $[\alpha]^{20.9}_D$ = −62.6 (c = 1.5, $CHCl_3$).

(*R*)-2-(1-Iodo-3-(2,2,2-trifluoroacetyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)ethyl 2,2,2-trifluoroacetate (9a). Trifluoroacetic anhydride (18.8 mL, 135.1 mmol) was added to an ice cold solution of alcohol **7** (9.68 g, 54.5 mmol) in dry diethyl ether (100 mL). After stirring for 2 h at room temperature, the solvent was removed under reduced pressure without external heating. The crude reaction mixture was dissolved in dry dichloromethane (100 mL). A solution of iodine monochloride (13.2 g, 81.1 mmol) in dichloromethane (50 mL) was added to the reaction mixture at 0 °C. After stirring for 2 h at room temperature, a solution of sodium thiosulfate (2M, 100 mL) was added and the mixture was stirred at room temperature. After 15 min, a saturated aqueous solution of sodium bicarbonate (100 mL) was added and stirring was continued for 15 min. The reaction mixture was filtered through a plug of Celite and washed with dichloromethane. The organic layer was separated, washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (300 g, 5% EtOAc/hexane) to give iodopyrrole **9a** (21.9 g, 81%) as a colorless oil: FTIR (neat, cm^{-1}) ν_{max} 2938, 1786, 1666, 1143; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (1H, q, J = 2.2 Hz), 5.73 (1H, dd, J = 14.7, 4.4 Hz), 4.40−4.26 (2H, m), 3.82 (1H, dd, J = 14.1, 12.5 Hz), 3.61−3.49 (1H, m), 2.35−2.21 (1H, m), 2.2−2.17 (6H, m), 1.6−1.5 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4 (q, J = 35.1 Hz), 157.3 (q, J = 42 Hz), 149.5, 130.7 (q, J = 4.4 Hz), 126.2, 118.0 (q, J = 289.4 Hz), 114.3 (q, J = 284 Hz), 68.0, 65.9, 46.9, 35.2, 29.8, 29.1, 28.2, 24.2; MS(GC) m/z (%) 497 (M^+, 40), 355 (100); HRMS calcd for $C_{15}H_{15}F_6INO_3$ (M^+ + H) 498.0001, found 498.0001; $[\alpha]^{21.4}_D$ = −70.0 (c = 5, $CHCl_3$).

(*R*)-2-(1-Iodo-3-(2,2,2-trichloroacetyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)ethyl 2,2,2-trichloroacetate (9b). A solution of iodine monochloride (5.4 g, 33.2 mmol) in dry dichloromethane (30 mL) was added slowly to a solution of trichloroacetate **8b** (12 g, 25.5 mmol) in dichloromethane (100 mL) at 0 °C. After stirring at room temperature for 14 h, a solution of sodium thiosulfate (2M, 100 mL) was added and the mixture was stirred at room temperature. After 10 min, a saturated aqueous solution of sodium bicarbonate (100 mL) was added and stirring was continued for 15 min. The reaction mixture was filtered through a plug of Celite and washed with dichloromethane. The organic layer was separated, washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure to give iodotrichloroacetate **9b** (13.7 g, 90%) as a purple foam, which was used without purification: FTIR (neat, cm^{-1}) ν_{max} 2929, 1763, 1665, 1240; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (1H, s), 5.56 (1H, dd, J = 14.9, 3.9 Hz), 4.51−4.32 (2H, m), 3.84 (1H, app. t, J = 13.5 Hz), 3.62−3.51 (1H, m), 2.37−1.31 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 161.9, 148.4, 130.5, 123.7, 96.2, 89.6, 67.4, 67.1, 47.0, 35.4, 29.9, 29.4, 28.2, 24.1; HRMS calcd for $C_{15}H_{15}Cl_6INO_3$ (M^+ + H) 593.8228, found 593.8226; $[\alpha]^{21.7}_D$ = −58.6 (c = 1, $CHCl_3$).

(*R*)-2,2,2-Trifluoro-1-(9-(2-hydroxyethyl)-1-iodo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)ethanone (10a). Poly(vinyl pyridine) resin (11.3 g) was added to a solution of trifluoroacetate **9a** (22.64 g, 45.5 mmol) in methanol (230 mL), and the mixture was stirred at room temperature. After 22 h, the reaction mixture was filtered through Celite and washed with ethyl acetate. The solvent was removed under reduced pressure to give alcohol **10a** (18.2 g, 99%) as a yellow oil, which was used without purification: FTIR (neat, cm^{-1}) ν_{max} 3351, 2931, 1661, 1479, 1140; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (1H, q, J = 1.4 Hz), 5.68 (1H, dd, J = 14.6, 4.5 Hz), 3.84 (1H, app. t, J = 13.3 Hz), 3.62 (1H, t, J = 4.9 Hz), 3.58−3.50 (1H, m), 2.2−1.48 (10H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0 (q, J = 34.4 Hz), 151.3, 130.7 (q, J = 4.3 Hz), 125.9, 116.9 (q, J = 289 Hz), 67.9, 60.5, 46.9, 34.8, 33.3, 29.9, 28.3, 24.2; MS (GC) m/z (%) 401 (M^+, 60), 355 (100), 230 (92); HRMS calcd for $C_{13}H_{16}F_3INO_2$ (M^+ + H) 402.0178, found 402.0178; $[\alpha]^{21.2}_D$ = −58.3 (c = 3, $CHCl_3$).

(*R*)-Methyl 9-(2-hydroxyethyl)-1-iodo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (10b). Sodium methoxide (2.04 g, 37.8 mmol) was added to a solution of iodotrichloroacetate **9b** (15 g, 25.2 mmol) in methanol (150 mL) at room temperature. After stirring for 8 h, the reaction mixture was quenched with water (100 mL). The mixture was extracted with ethyl acetate (2 × 500 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to give hydroxy methyl ester pyrrole **10b** (8.3 g, 90%) as a yellow oil, which was used without purification: FTIR (neat, cm^{-1}) ν_{max} 3367, 1698, 1512, 1149; ^1H NMR (400 MHz, $CDCl_3$) 6.96 (1H, s), 5.66 (1H, dd, J = 14.7, 4.1 Hz), 3.76 (3H, s), 3.79−3.72 (1H, m), 3.59 (2H, t, J = 5.9 Hz), 3.85−3.40 (1H, m), 2.12−1.18 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 144.9, 124.5, 123.5, 65.0, 60.8, 51.2, 46.1, 34.6, 33.9, 30.8, 28.9, 24.6; MS (ESI+) m/z (%) 364 (M^+ + 1, 100), 279 (20), 210 (54); HRMS calcd for $C_{13}H_{19}INO_3$ (M^+ + H) 364.0410, found 364.0409; $[\alpha]^{20.8}_D$ = −33.8 (c = 1.1, $CHCl_3$).

(*R*)-1-(9-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-1-iodo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)-2,2,2-trifluoroethanone (11a). Imidazole (4.63 g, 68.1 mmol) and *tert*-butyl dimethyl silyl chloride (10.25 g, 68.1 mmol) were added to an ice cold solution of alcohol **10a** (18.2 g, 45.4 mmol) in dry dichloromethane (200 mL). After stirring at room temperature for 3 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (200 mL) and mixture was extracted with dichloromethane (2 × 300 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure to give trifluoroethanone **11a** (23.3 g, 99%) as a yellow oil, which was used without purification: FTIR (neat, cm^{-1}) ν_{max} 2930, 1665, 1242, 1141; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (1H, q, J = 2.3 Hz), 5.67 (1H, dd, J = 14.0, 4.8 Hz), 3.87 (1H, dd, J = 13.7, 12.3 Hz), 3.72−3.65 (1H, m), 3.62−3.47 (2H, m), 2.08−1.75 (6H, m), 1.7−1.43 (2H, m), 0.88 (9H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9 (q, J = 35.4 Hz), 152.1, 130.8, 125.7, 117.0 (q, J = 293.2 Hz), 67.7, 60.8, 46.7, 35.1, 33.3, 29.2, 28.3, 25.9 (3C), 24.2, 18.2, −5.4, −5.5; HRMS calcd for $C_{19}H_{30}F_3INO_2Si$ (M^+ + H) 516.1043, found 516.1040; $[\alpha]^{21.3}_D$ = −67.4 (c = 5, $CHCl_3$).

(*R*)-Methyl 9-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1-iodo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (11b). Imidazole (2.36 g, 34.7 mmol) and *tert*-butyl dimethyl silyl chloride (5.23 g, 34.7 mmol) were added to an ice cold solution of hydroxy methyl ester pyrrole **10b** (8.4 g, 23.14 mmol) in dry dichloromethane (80 mL). After stirring at room temperature for 5 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (100 mL) and the mixture was extracted with dichloromethane

(2 × 200 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (150 g, 10% EtOAc/hexane) to give pyrrole TBS ether **11b** (8.83 g, 80%) as a colorless oil: FTIR (neat, cm^{-1}) ν_{max} 2927, 1702, 1094; ^1H NMR (500 MHz, $CDCl_3$) δ 6.96 (1H, s), 5.65 (1H, dd, J = 11.6, 4.0 Hz), 3.77 (3H, s), 3.82−3.36 (4H, m), 2.12−1.36 (8H, m), 0.88 (9H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 145.7, 124.6, 123.2, 64.7, 61.3, 51.1, 46.1, 34.7, 34.0, 30.1, 29.0, 26.0 (3C), 24.6, 18.3, −5.2, −5.3; HRMS calcd for $C_{19}H_{33}INO_3Si$ (M^+ + H) 478.1274, found 478.1274; $[\alpha]^{21.7}_D$ = −37.4 (c = 2.5, $CHCl_3$).

(*R*)-1-(9-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-1-(3-hydroxyprop-1-ynyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)-2,2,2-trifluoroethanone (12a). To a stirred solution of iodopyrrole **11a** (17.7 g, 34.36 mmol) and propargyl alcohol (8.2 mL, 137.4 mmol) in DME (200 mL) were added at room temperature copper(I) iodide (1.3 g, 6.87 mmol), potassium carbonate (18.9 g, 137.4 mmol), palladium on carbon (10%, 910 mg, 0.85 mmol), and triphenyl phosphine (901 mg, 3.4 mmol). After degassing with nitrogen gas for 30 min, the reaction mixture was heated to 85 °C and stirred for 16 h under nitrogen. The mixture was allowed to cool to rt, filtered through Celite, and washed with ethyl acetate. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (300 g, 10% EtOAc/hexane) to give propargyl alcohol **12a** (13.2 g, 87%) as a pale yellow oil: FTIR (neat, cm^{-1}) ν_{max} 3412, 2930, 2233, 1665, 1142; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (1H, q, J = 1.9 Hz), 5.34 (1H, br s), 4.42 (2H, d, J = 5.3 Hz), 4.08 (1H, s), 3.74−3.48 (3H, m), 2.37 (1H, t, J = 5.7 Hz), 2.16−1.48 (8H, m), 0.85 (9H, s), 0.06 (3H, s), 0.013 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4 (q, J = 35 Hz), 154.2, 126.8 (q, J = 4 Hz), 122.8, 117.0 (q, J = 289 Hz), 105.8, 89.4, 78.8, 61.2, 51.5, 46.6, 33.7, 33.5, 29.9, 28.0, 25.8 (3C), 25.0, 18.2, −5.4, −5.5; HRMS calcd for $C_{22}H_{33}F_3NO_3Si$ (M^+ + H) 444.2182, found 444.2184; $[\alpha]^{20.6}_D$ = −69.5 (c = 3, $CHCl_3$).

(*R*)-Methyl 9-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1-(3-hydroxyprop-1-ynyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (12b). To a stirred solution of pyrrole TBS ether **11b** (3 g, 6.29 mmol) and propargyl alcohol (1.11 mL, 18.86 mmol) in DMSO (20 mL) were added at room temperature copper(I) iodide (119 mg, 0.62 mmol), triethylamine (2.62 mL, 18.86 mmol), and $PdCl_2(PPh_3)_2$ (221 mg, 0.314 mmol). After degassing with nitrogen gas for 30 min, the reaction mixture was heated to 50 °C and stirred for 28 h under nitrogen. The mixture was allowed to cool to rt, diluted with ethyl acetate (100 mL), filtered through Celite, and washed with ethyl acetate. The filtrate was washed with water (3 × 200 mL) and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (200 g, 20% EtOAc/hexane) to give pyrrole propargyl alcohol **12b** (1.53 g, 60%) as a pale yellow oil: FTIR (neat, cm^{-1}) ν_{max} 3430, 2928, 2230, 1703, 1156; ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (1H, s), 5.3 (1H, br s), 4.42 (2H, s), 4.0 (1H, br s), 3.76 (3H, s), 3.75−3.38 (3H, m), 2.16−1.45 (9H, m), 0.87 (9H, s), 0.02 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 148.4, 120.6, 120.4, 102.5, 88.0, 80.5, 61.5, 51.8, 51.1, 45.9, 34.2, 33.2, 30.8, 28.6, 25.9 (3C), 25.4, 18.3, −5.3, −5.4; HRMS calcd for $C_{22}H_{36}NO_4Si$ (M^+ + H) 406.2414, found 406.2417; $[\alpha]^{21.0}_D$ = −25.4 (c = 0.9, $CHCl_3$).

(*R*)-1-(1-(3-Bromoprop-1-ynyl)-9-(2-(*tert*-butyldimethylsilyloxy)ethyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)-2,2,2-trifluoroethanone (13a). To a stirred solution of propargyl alcohol **12a** (12.9 g, 29.1 mmol) and 2,4,6-collidine (5.8 mL, 43.7 mmol) in dry dichloromethane (130 mL) was added 5 Å molecular sieves (13 g) under an inert atmosphere. After stirring for 15 min at room temperature, the reaction mixture was cooled to 0 °C. A stirred solution of carbon tetrabromide [90% (6% water), 16.1 g, 43.7 mmol] in dry dichloromethane (100 mL) predried over 5 Å molecular sieves (16 g) was added slowly to the reaction mixture at 0 °C, followed by a solution of triphenyl phosphine (9.16 g, 34.9 mmol) in dichloromethane (50 mL). After stirring at 0 °C for 1 h, the reaction mixture was filtered through Celite and washed with dichloromethane. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (300 g, 5% EtOAc/hexane) to give propargyl bromide **13a** (12.2 g, 83%) as a pale yellow solid: mp 45−47 °C; FTIR (neat, cm^{-1}) ν_{max} 2929, 2232, 1668, 1147, 1145; ^1H NMR (400 MHz, $CDCl_3$) δ 7.2 (1H, q, J = 1.8 Hz), 5.42 (1H, br d, J = 7.8 Hz), 4.14 (2H, s), 4.04 (1H, app. t, J = 13.3 Hz), 3.74−3.50 (4H, m), 2.14−2.05 (1H, m), 1.95−1.48 (6H, m), 0.86 (s, 9H), 0.025 (3H), 0.02 (3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (q, J = 34.3 Hz), 154.6, 126.8 (q, J = 3.8 Hz), 122.9, 116.9 (q, J = 289.5 Hz), 105.4, 86.2, 80.3, 61.1, 46.7, 33.6 (2C), 29.8, 28.0, 25.8 (3C), 24.9, 18.2, 15.6, −5.4, −5.5; HRMS calcd for $C_{22}H_{32}BrF_3NO_2Si$ (M^+ + H) 506.1338, found 506.1378; $[\alpha]^{20.5}_D$ = −61.9 (c = 3, $CHCl_3$).

(*R*)-Methyl 1-(3-bromoprop-1-ynyl)-9-(2-(*tert*-butyldimethylsilyloxy)ethyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (13b). To a stirred solution of pyrrole propargyl alcohol **12b** (500 mg, 1.23 mmol) and 2,4,6-collidine (244 μL, 1.85 mmol) in dry dichloromethane (5 mL) was added 5 Å molecular sieves (1 g) under an inert atmosphere. After stirring for 15 min at room temperature, the reaction mixture was cooled to 0 °C. A stirred solution of carbon tetrabromide [90% (6% water), 546 mg, 1.48 mmol] in dry dichloromethane (3 mL) predried over 5 Å molecular sieves (2 g) was added slowly to the reaction mixture at 0 °C, followed by a solution of triphenyl phosphine (388 mg, 1.48 mmol) in dichloromethane (3 mL). After stirring at 0 °C for 1 h, the reaction mixture was filtered through Celite and washed with dichloromethane. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (20 g, 5% EtOAc/hexane) to give pyrrole propargyl bromide **13b** (329 mg, 57%) as a pale yellow oil: FTIR (neat, cm^{-1}) ν_{max} 2950, 2225, 1707, 1475, 1158; ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (1H, s), 5.38 (1H, br s), 4.16 (2H, s), 3.94 (1H, br s), 3.76 (3H, s), 3.72−3.41 (3H, m), 2.12−1.48 (8H, m), 0.87 (9H, s), 0.02 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 149.0, 120.8, 120.5, 102.3, 85.0, 82.3, 61.5, 51.1, 46.0, 34.1, 33.2, 30.6, 28.6, 25.9 (3C), 25.3, 18.2, 16.5, −5.3, −5.4; HRMS calcd for $C_{22}H_{35}BrNO_3Si$ (M^+ + H) 468.1570, found 468.1581; $[\alpha]^{21.0}_D$ = −11.2 (c = 5.0, $CHCl_3$).

(*R*)-Methyl 9-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1-(3-chloroprop-1-ynyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (14). Triethylamine (185 μL, 1.33 mmol) followed by methanesulfonyl chloride (77 μL, 1.0 mmol) was added to an ice cold solution of pyrrole propargyl alcohol **12b** (270 mg, 0.66 mmol) in dry dichloromethane (3 mL), and the mixture was stirred for 1 h. A saturated aqueous NH_4Cl solution (20 mL) was added, and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (15 g, 10% EtOAc/hexane) to give chloropyrrole **14** (28 mg, 10%) as a pale yellow oil: FTIR (neat, cm^{-1}) ν_{max} 2928, 2229, 1703, 1157; ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (1H, s), 5.38 (1H, br s), 4.36 (2H, s), 3.94 (1H, br s), 3.76 (3H, s), 3.74−3.39 (3H, m), 2.12−1.41 (8H, m), 0.87 (9H, s), 0.02 (3H, s), 0.017 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 148.9, 120.7, 120.5, 102.2, 84.6, 81.6, 61.4, 51.1, 46.0, 34.1, 33.2, 31.9, 30.6, 28.6, 25.9 (3C), 25.2, 18.2, −5.38, −5.4; MS (GC) m/z (%) 423 (M^+, 10), 387 (30), 330 (40), 278 (72), 256 (100); HRMS calcd for $C_{22}H_{35}ClNO_3Si$ (M^+ + H) 424.2075, found 424.2065; $[\alpha]^{21.5}_D$ = −14.0 (c = 3.0, $CHCl_3$).

(*R*)-1-(9-(2-Bromoethyl)-1-(3-bromoprop-1-ynyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)-2,2,2-trifluoroethanone (15): FTIR (neat, cm^{-1}) ν_{max} 2932, 2232, 1669, 1143;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (1H, q, J = 2.0 Hz), 5.38 (1H, br d, J = 10.6 Hz), 4.16 (2H, s), 4.06 (1H, app. t, J = 12.3 Hz), 3.65−3.58 (1H, m), 3.51−3.32 (2H, m), 2.58−2.41 (1H, m), 2.26−2.10 (1H, m), 2.0−1.4 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (q, J = 35.0 Hz), 152.5, 126.6 (q, J = 4.2 Hz), 123.3, 120.7 (q, J = 289 Hz), 105.9, 86.8, 79.9, 46.8, 35.7, 34.4, 30.9, 30.3, 27.9, 25.1, 15.5; HRMS calcd for $C_{16}H_{17}F_3Br_2NO$ (M^+ + H) 453.9629, found 453.9630; $[\alpha]^{20.7}_D$ = −97.3 (c = 1.25, $CHCl_3$).

(*R*)-1-(1-(3-Bromoprop-1-ynyl)-9-(2-hydroxyethyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)-2,2,2-trifluoroethanone (16). Amberlyst-15 (8.5 g) was added to a stirred mixture of propargyl bromide **13a** (8.5 g, 16.8 mmol) and 5 Å molecular sieves (16 g) in freshly distilled isopropyl alcohol (250 mL) under an inert atmosphere. After 24 h, the reaction mixture was filtered through Celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to give alcohol **16** (5.91 g, 90%) as a purple oil, which was used without purification: FTIR (neat, cm^{-1}) ν_{max} 3467, 2930, 2232, 1665; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (1H, q, J = 1.8 Hz), 5.51 (1H, br d, J = 10.1 Hz), 4.16 (2H, s), 3.94 (1H, app. t, J = 12.1 Hz), 3.74−3.54 (3H, m), 2.2−1.45 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (q, J = 35.4 Hz), 154.0, 126.3, 123.0, 117 (q, J = 292.1 Hz), 105.5, 86.5, 80.1, 60.3, 46.8, 33.4, 33.0, 30.2, 27.8, 24.7, 15.5; HRMS calcd for $C_{16}H_{18}BrF_3NO_2$ (M^+ + H) 392.0473, found 392.0478; $[\alpha]^{21.1}_D$ = −79.9 (c = 3, $CHCl_3$).

(*R*)-2,2,2-Trifluoro-1-(1-(3-fluoroprop-1-ynyl)-9-(2-hydroxyethyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)-ethanone (17). Tetra-*n*-butylammonium fluoride (37 mg, 0.118 mmol) was added to a solution of propargyl bromide **13a** (50 mg, 0.098 mmol) in THF (1 mL) at room temperature. After stirring 14 h, the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (5 mL). The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (5 g, 20% EtOAc/hexane) to give propargylic fluoride **17** (15 mg, 48%) as a purple oil: FTIR (neat, cm^{-1}) ν_{max} 3418, 2932, 2235, 1656, 1263; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (1H, q, J = 1.8 Hz), 5.53 (1H, br d, J = 9.2 Hz), 5.16 (2H, d, J = 48.5 Hz), 3.94 (1H, t, J = 12.3 Hz), 3.75−3.48 (3H, m), 2.17−1.48 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (q, J = 34.3 Hz), 153.9, 126.7, 123.3, 116.9 (q, J = 290 Hz), 105.3, 85.2 (d, J = 21.0 Hz), 83.1 (d, J = 11.4 Hz), 71.1 (d, J = 164.1 Hz), 60.6, 47.0, 33.6, 33.1, 30.5, 28.0, 24.9; HRMS calcd for $C_{16}H_{18}F_4NO_2$ (M^+ + H) 332.1274, found 332.1276; $[\alpha]^{21}_D$ = −88.5 (c = 1, $CHCl_3$).

(*R*)-2-(1-(3-Bromoprop-1-ynyl)-3-(2,2,2-trifluoroacetyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)acetaldehyde (18). Dess−Martin periodinane (8.6 g, 20.3 mmol) was added to an ice cold solution of bromoalcohol **16** (6.1 g, 15.6 mmol) in dry dichloromethane (60 mL) under nitrogen. After stirring at room temperature for 3 h, solvent was removed under reduced pressure without external heating. The residue was taken up in diethyl ether (150 mL) and stirred for 15 min. The mixture was filtered through a short pad of Celite and silica gel and washed with diethyl ether. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (300 g, 15% EtOAc/hexane) to give bromoaldehyde **18** (5.09 g, 84%) as a colorless oil: FTIR (neat, cm^{-1}) ν_{max} 2934, 2232, 1723, 1664, 1538, 1131; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (1H, s), 7.20 (1H, q, J = 2.3 Hz), 5.1−4.4 (2H, m), 4.15 (2H, s), 3.9 (1H, br s), 3.28−3.12 (1H, m), 2.9 (1H, dd, J = 17.6, 7.6 Hz), 1.90−1.68 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 169.7 (q, J = 34.3 Hz), 151.8, 127.1, 123.0, 116.7 (q, J = 290 Hz), 104.1, 86.9, 80.1, 46.4, 45.2, 31.5, 30.7, 27.4, 26.1, 15.4; HRMS calcd for $C_{16}H_{16}BrF_3NO_2$ (M^+ + H) 390.0316, found 390.0314; $[\alpha]^{21}_D$ = −53.4 (c = 10, $CHCl_3$).

2,2,2-Trifluoro-1-((9*S*,10a*R*)-9-hydroxy-8-vinylidene-1,2,3,4,8,9,10,10*a*-octahydroazepino[3,2,1-*hi*]indol-6-yl)ethanone (19). Acetic acid (70 mL) was added to a solution of bromoaldehyde **18** (7.1 g, 18.2 mmol) in DMF (70 mL) at −40 °C under nitrogen, followed by indium (8.38 g, 73.0 mmol). After stirring at the same temperature for 20 h, the reaction mixture was warmed to room temperature. Approximately two-thirds of the solvent was removed by distillation at 30 °C under reduced pressure (0.8 Torr). The residue was poured into ice−water (200 mL). The resulting precipitate was filtered, washed with water, and then dried. The crude compound was purified by flash column chromatography on silica gel (300 g, 80% CH_2Cl_2/hexane) to give allenic alcohol **19** (2.95 g, 52%) as a colorless solid: mp 160−162 °C; FTIR (KBr, cm^{-1}) ν_{max} 3265, 1948, 1670, 1500, 1456, 1265; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (1H, q, J = 2.1 Hz), 5.59 (1H, dd, J = 14.3, 6.0 Hz), 5.38 (1H, dd, J = 11.3, 3.5 Hz), 5.31 (1H, dd, J = 11.3, 3.6 Hz), 4.52−4.42 (1H, m), 3.66 (1H, dd, J = 13.9, 3.6 Hz), 2.95 (1H, dd, J = 16.4, 8.3 Hz), 2.4−2.31(1H, m), 2.14−2.0 (1H, m), 1.95 (1H, d, J = 4.1 Hz), 1.93−1.91 (1H, m), 1.84−1.50 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 169.7 (q, J = 34.5 Hz), 147.3, 124.7, 120.0 (q, J = 4.0 Hz), 117.1 (q, J = 289 Hz), 115.7, 102.1, 83.1, 66.8, 47.8, 39.3, 35.0, 34.2, 30.1, 27.8; MS (GC) m/z (%) 311 (M^+, 100), 242 (34), 214 (92), 186 (34), 172 (32); HRMS calcd for $C_{16}H_{17}F_3NO_2$ (M^+ + H) 312.1211, found 312.1213; $[\alpha]^{21}_D$ = 7.7 (c = 1, $CHCl_3$).

(9*S*,10a*R*)-9-Hydroxy-8-vinylidene-1,2,3,4,8,9,10,10a-octahydroazepino[3,2,1-*hi*]indole-6-carboxylic acid (20). NaOH (2 M aq., 13.3 mL, 26.5 mmol) was added slowly to a solution of allenic alcohol **19** (2.75 g, 8.84 mmol) in DMSO (30 mL) at 15 °C. After stirring at room temperature for 15 min, the reaction mixture was poured into ice−water (300 mL) and acidified with 2 M citric acid. The resulting precipitate was filtered, washed with water, and then dried to afford the carboxylic acid **20** as a pale yellow solid (2.06 g, 90%): mp 152−154 °C; FTIR (KBr, cm^{-1}) ν_{max} 3283, 2353, 1946, 1684, 1491, 1460; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.1(1H, br s), 6.54 (1H, s), 5.44 (1H, br d, J = 10.4 Hz), 5.16 (1H, dd, J = 10.9, 3.5 Hz), 5.12 (1H, dd, J = 10.9, 3.5 Hz), 5.03 (1H, d, J = 5.0 Hz), 4.27 (1H, br s), 3.57 (1H, app. t, J = 12.1 Hz), 2.92 (1H, dd, J = 16.0, 8.8 Hz), 2.2−1.75 (4H, m), 1.59 (2H, app. q, J = 10 Hz), 1.35 (2H, app. quint, J = 12.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 203.5, 162.1, 140.9, 122.2, 112.9, 112.7, 103.0, 80.4, 66.1, 46.0, 40.4, 35.4, 33.6, 29.6, 28.0; HRMS calcd for $C_{15}H_{18}NO_3$ (M^+ + H) 260.1287, found 260.1290; $[\alpha]^{21.5}_D$ = 55.1 (c = 0.5, CH_3OH).

Butenolide (21). Triruthenium dodecacarbonyl (9 mg, 0.014 mmol) was added to a mixture of allenic alcohol **19** (90 mg, 0.289 mmol) and triethylamine (120 μL, 0.868 mmol) in dioxane (2 mL) at room temperature in a Fisher-Porter tube. The tube was flushed with carbon monoxide and pressurized to 100 psi, then stirred at 100 °C for 14 h. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (10 g, 20% EtOAc/hexane) to give lactone **21** (85 mg, 87%) as a yellow solid: mp 114−116 °C; FTIR (neat, cm^{-1}) ν_{max} 2930, 1747, 1666, 1531, 1265; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, q, J = 1.8 Hz), 5.60 (1H, dd, J = 14.4, 5.7 Hz), 4.86−4.75 (1H, m), 3.74 (1H, dd, J = 14.0, 11.2 Hz), 3.14−3.05 (1H, m), 2.79−2.67 (1H, m), 2.21−1.8 (3H, m), 2.04 (3H, d, J = 1.8 Hz), 1.85−1.42 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 170.3 (q, J = 34.5 Hz), 151.7, 149.7, 125.9, 119.6 (q, J = 3.8 Hz), 116.8 (q, J = 292.2 Hz), 116.2, 114.3, 71.1, 48.6, 36.7, 35.2, 34.3, 29.3, 27.0, 9.1; MS (ESI+) m/z (%) 340 (M^+ + 1, 100), 287 (16), 190 (27); HRMS calcd for $C_{17}H_{17}F_3NO_3$ (M^+ + H) 340.1161, found 340.1160; $[\alpha]^{21.1}_D$ = −96.8 (c = 1.5, $CHCl_3$).

Lactone (22). Triruthenium dodecacarbonyl (50 mg, 0.077 mmol) was added to a mixture of allenic acid **20** (500 mg, 1.93 mmol) and 2,4,6-collidine (1.53 mL, 11.6 mmol) in dioxane (20 mL) at room temperature in a Fisher-Porter tube. The tube was flushed with carbon monoxide and pressurized to 100 psi, then stirred at 100 °C for 14 h. The reaction

mixture was cooled to 0 °C and acidified with 0.5 M of HCl. The reaction mixture was diluted with 50 mL of water and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (30 g, 40% EtOAc/hexane, 0.05% of acetic acid) to give lactone **22** (376 mg, 68%) as a purple foam: FTIR (KBr, cm^{-1}) ν_{max} 3470, 2924, 1747, 1664, 1161; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, s), 5.59 (1H, dd, J = 14.0, 5.2 Hz), 4.88−4.70 (1H, m), 3.67 (1H, dd, J = 13.8, 11.0 Hz), 3.12−3.0 (1H, m), 2.76−2.66 (1H, m), 2.2−1.93 (3H, m), 2.04 (3H, d, J = 5.6 Hz), 1.79−1.38 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 165.4, 153.3, 145.7, 123.5, 116.0, 114.6, 112.7, 77.4, 47.9, 37.1, 35.7, 34.5, 29.6, 27.6, 8.9; HRMS calcd for $C_{16}H_{18}NO_4$ (M^+ + H) 288.1236, found 288.1239; $[\alpha]^{21.1}_D$ = −81.0 (c = 1.1, $CHCl_3$).

(*R,E*)-8-Ethylidene-9-oxo-1,2,3,4,8,9,10,10a-octahydroazepino[3,2,1-*hi*]indole-6-carboxylic acid (23): Mp 176−178 °C; FTIR (KBr, cm^{-1}) ν_{max} 3150, 1689, 1602, 1469; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (1H, s), 6.25 (1H, q, J = 7.6 Hz), 5.44 (1H, dd, J = 14.2, 5.4 Hz), 3.73 (1H, dd, J = 14.4, 11.2 Hz), 3.27−3.16 (1H, m), 2.92 (1H, dd, J = 14.8, 7.2 Hz), 2.55 (1H, dd, J = 15.0, 6.2 Hz), 2.12 (3H, d, J = 7.6 Hz), 2.08−1.41 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 166.0, 141.1, 129.4, 128.1, 121.9, 120.1, 113.2, 47.7, 46.2, 35.1, 34.7, 29.5, 28.2, 15.3; MS (ESI+) m/z (%) 260 (M^+ + 1, 100), 216 (92), 181 (42); HRMS calcd for $C_{15}H_{18}NO_3$ (M^+ + H) 260.1287, found 260.1283; $[\alpha]^{21.3}_D$ = −35.7 (c = 1.4, $CHCl_3$).

Pyrrole (24). Trifluoroacetic acid (340 μL, 8.71 mmol) was added to a solution of acid **22** (500 mg, 1.74 mmol) in dichloromethane (8 mL) under nitrogen at room temperature. The reaction mixture was heated to 40 °C. After 4 h heating, the reaction mixture was cooled to room temperature and quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (15 g, 15% EtOAc/hexane) to give pyrrole **24** (381 mg, 90%) as a pale yellow solid: mp 170−172 °C; FTIR (KBr, cm^{-1}) ν_{max} 2930, 1744, 1664, 1294; ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (1H, d, J = 2.9 Hz), 6.29 (1H, d, J = 2.9 Hz), 4.87−4.73 (1H, m), 4.15−4.05 (1H, m), 3.88−3.77 (1H, m), 3.03−2.92 (1H, m), 2.68−2.59 (1H, m), 2.18−2.02 (2H, m), 2.0 (3H, d, J = 1.2 Hz), 1.98−1.87 (1H, m), 1.72−1.32 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 155.2, 137.6, 124.9, 113.2, 111.7, 103.8, 77.8, 51.7, 37.8, 36.4, 34.7, 29.6, 28.7, 8.8; MS (ESI+) m/z (%) 244 (M^+ + 1, 100); HRMS calcd for $C_{15}H_{18}NO_2$ (M^+ + H) 244.1338, found 244.1338; $[\alpha]^{20.6}_D$ = −152.9 (c = 1.0, $CHCl_3$).

Lactone (2). Magnesium powder (30 mg, 1.23 mmol) was added to a solution of pyrrole **24** (30 mg, 0.123 mmol) in dry methanol (2 mL) under nitrogen at room temperature. After stirring for 24 h, the reaction mixture was quenched with 1 M of HCl (5 mL). The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (5 g, 15% EtOAc/hexane) to give lactone **2** (13.5 mg, 45%) as a colorless solid: mp 122−124 °C; FTIR (neat, cm^{-1}) ν_{max} 2928, 1768, 1004; ^1H NMR (400 MHz, $CDCl_3$) δ 6.51 (1H, d, J = 2.6 Hz), 5.94 (1H, d, J = 2.7 Hz), 4.72 (1H, m, ddd, J = 11.8, 7.3, and 4.6 Hz), 4.05 (1H, dd, J = 13.8, 5.2 Hz), 3.77 (1H, dd, J = 13.7, 11.4 Hz), 3.13 (1H, d, J = 10.8, 7.7 Hz), 2.82−2.72 (1H, m), 2.58−2.48 (1H, m), 2.29 (1H, ddd, J = 13.0, 10.0, and 5.0 Hz), 2.18−1.85 (3H, m), 1.73−1.52 (3H, m), 1.4 (3H, d, J = 7.1 Hz), 1.38−1.21 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7, 131.9, 122.5, 116.5, 104.9, 76.8, 51.4, 42.1, 41.7, 36.5, 35.2, 33.4, 30.1, 29.5. 14.0; MS (ESI+) m/z (%) 246 (M + 1, 100), 197 (48); HRMS calcd for $C_{15}H_{20}NO_2$ (M^+ + H) 246.1494, found 246.1490; $[\alpha]^{21.1}_D$ = −1.11 (c = 0.7, $CHCl_3$).

Minor Isomer (25): FTIR (neat, cm^{-1}) ν_{max} 2931, 1767, 1175; ^1H NMR (400 MHz, $CDCl_3$) δ 6.48 (1H, d, J = 2.7 Hz), 5.87 (1H, d, J = 2.7 Hz), 4.79 (1H, ddd, J = 9.5, 6.1, and 3.4 Hz), 3.97 (1H, dd, J = 13.9, 5.2 Hz), 3.80 (1H, app. t, J = 12.5 Hz), 3.61 (1H, app. t, J = 7.0 Hz), 3.10−2.91(1H, m), 2.82−2.72 (1H, m), 2.28−2.13 (1H, m), 2.11−2.01 (2H, m), 1.98−1.82 (2H, m), 1.59−1.35 (3H, m), 1.31 (3H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 132.8, 120.9, 111.0, 104.9, 77.9, 50.0, 40.8, 38.4, 36.7, 34.2, 32.0, 30.8, 29.4, 12.6; MS (ESI+) m/z (%) 246 (M^+ + 1, 100); HRMS calcd for $C_{15}H_{20}NO_2$ (M^+ + H) 246.1494, found 246.1495; $[\alpha]^{21.6}_D$ = 22.1 (c = 0.7, $CHCl_3$).

Dimer (26): Colorless solid; mp 242−244 °C; FTIR (neat, cm^{-1}) ν_{max} 2932, 1772; ^1H NMR (400 MHz, $CDCl_3$) δ 6.49 (1H, d, J = 2.8 Hz), 5.96 (1H, d, J = 2.8 Hz), 4.35 (1H, dd, J = 8.0, 3.5 Hz), 4.0 (1H, dd, J = 14.2, 5.2 Hz), 3.86 (1H, app. t, J = 11.6 Hz), 3.40 (1H, q, J = 7.5 Hz), 2.78−2.62 (1H, m), 2.44−1.38 (8H, m), 1.33 (3H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 133.9, 121.7, 113.2, 107.7, 80.8, 54.0, 50.2, 43.5, 36.5, 36.3, 31.5, 29.5, 28.8, 16.1; MS (ESI+) m/z (%) 489 (M^+ + 1, 100); HRMS calcd for $C_{30}H_{37}N_2O_4$ (M^+ + H) 489.2753, found 489.2751; $[\alpha]^{21.1}_D$ = 137.6 (c = 0.4, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra for compounds **2**−**26** and chiral HPLC for compound **7**. CIFs for compounds **2**, **13a**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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