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Total Synthesis of Pinnamine and Anatoxin-a via a Common Intermediate. A Caveat on the Anatoxin-a Endgame

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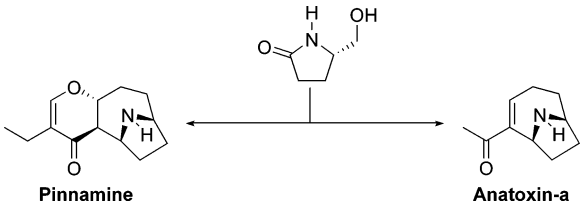

This paper describes the total synthesis of the naturally occurring alkaloids pinnamine (**1**) and anatoxin-a (**2**) from a common enantiomerically pure intermediate (**7**) easily available from pyroglutamic acid. The synthesis of enantiopure pinnamine proceeded in 10 steps and 4.8% overall yield, and the route was flexible enough to allow stereocontrolled access to a non-natural congener (5-*epi*-pinnamine) of the natural product. Intramolecular reaction of an *N*-acyl iminium ion was a key step in the synthesis of both pinnamine and anatoxin-a. However, in stark contrast to literature precedent, complete racemization was observed during the reaction of the *N*-acyliminium ion leading to the latter alkaloid.

Introduction

Pinnamine **1** and anatoxin-a **2** are two potent alkaloidal toxins possessing the unusual 9-azabicyclo[4.2.1]-nonane skeleton. Pinnamine (shown in Figure 1 using the numbering used in the literature) was isolated from the Okinawan bivalve *Pinna muricata* and characterized in 2000,[1] and a 16-step total synthesis of the naturally occurring enantiomer appeared the following year.[2] This alkaloid shows characteristic toxic symptoms, resembling those of anatoxin-a,[1a,2] such as acute toxicity against mice with a LD_{99} (intraperitoneal, mouse) of 0.5 mg/kg resulting in death within 5 min, and can be regarded as a conformationally constrained version of anatoxin-a.[3]

Anatoxin-a was reported in 1977,[4] and the structure was established by X-ray crystallographic analysis.[5] It

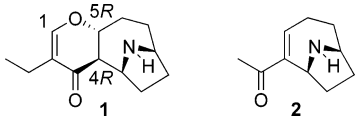

FIGURE 1. Pinnamine **1** (numbering as in the literature)[1a,2] and anatoxin-a **2**.

is a potent neurotoxin produced by certain strains of the freshwater blue green alga *Anabena flos-aquae* and has been responsible for fatal poisoning of wildlife in North America. Anatoxin-a is also known as "Very Fast Death Factor" and causes death by respiratory paralysis with an LD_{50} (intraperitoneal, mouse) of 0.2 mg/kg.[6] The alkaloid mimics the neurotransmitter acetylcholine and therefore acts as a potent agonist for the nicotinic acetylcholine receptor nAChR.[7] As acetylcholine deficiency is implicated in diseases such as Alzheimer's, analogues of anatoxin-a possessing lower levels of toxicity may have potential in the treatment of brain disorders.[8] The combination of unusual structure and significant biological properties has prompted much synthetic inter-

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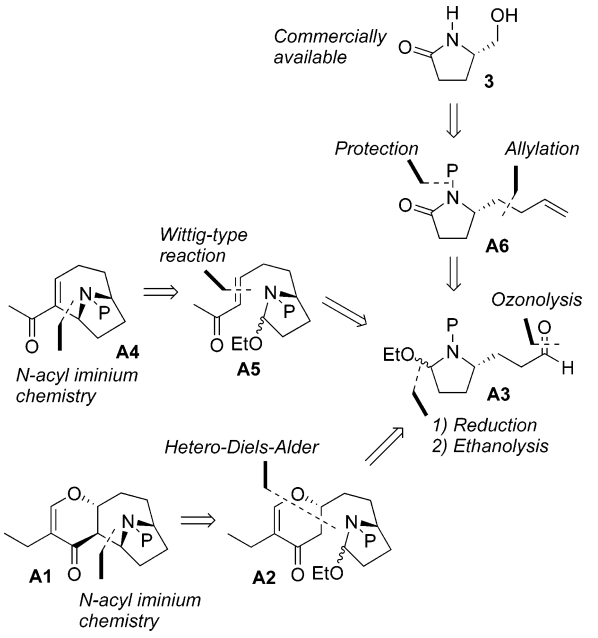
SCHEME 1. Retrosynthetic Analysis of Protected Pinnamine A1 and Protected Anatoxin-a A4[a]

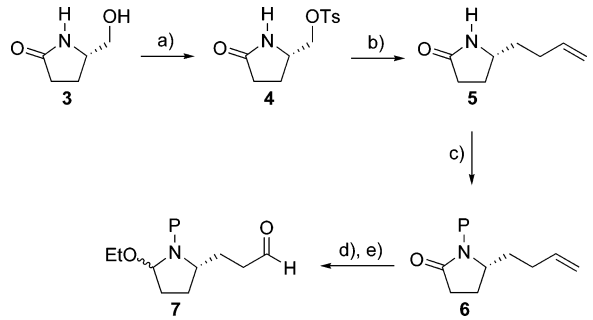


[a] P = protecting group.

est and numerous total syntheses of racemic and enantiomerically pure anatoxin-a have appeared.[9] In this paper, we present total syntheses of both pinnamine and anatoxin-a from a common chiral intermediate (Scheme 1). As will become apparent, this plan provided an unpleasant surprise en route to the latter alkaloid.

The combined retrosynthetic scheme for both *N*-protected pinnamine **A1** and *N*-protected anatoxin-a **A4** is shown in Scheme 1. The key idea for the synthesis of **A1** was to obtain the dihydropyrone **A2** by an asymmetric hetero-Diels−Alder reaction between aldehyde **A3** and an appropriate silyloxydiene. Generation of an iminium ion followed by cyclization would then yield the protected pinnamine derivative **A1**. Aldehyde **A3** could be derived from alkene **A6** which in turn could be synthesized from the commercially available and enantiomerically pure pyroglutamic acid derivative **3**. Aldehyde **A3** would be the branching point for the syntheses of **A1** and **A4** since similar intermediates have been used previously in both enantiomerically pure (P = Ts)[10] and racemic (P = CO_2Me)[11] form for the synthesis of anatoxin-a. Thus, for both **A1** and **A4** the final ring-closure step was projected to involve *N*-acyliminium ion intermediates.[12]

SCHEME 2[a]



[a] P = CO_2Me. Key: (a) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 98%; (b) allylmagnesium chloride, THF/Et_2O 1:1, 0 °C to rt, 51%; (c) *n*-BuLi, $ClCO_2Me$, THF, −78 to 0 °C, 91%; (d) $NaBH_4$, little H_2SO_4, EtOH, −20 °C; then excess H_2SO_4, EtOH, 0 °C; (e) O_3, CH_2Cl_2, −78 °C; then PPh_3, CH_2Cl_2, −78 °C to rt, two steps, 68%.

Results and Discussion

The synthesis of pinnamine started with the conversion of **3** to tosylate **4** in 98% yield (Scheme 2).[13] Next, the allyl group was installed, yielding alkene **5**. Although the yield was moderate (51%), this method is very direct and could be reproduced without difficulty on a multigram scale. It is noteworthy that the direct displacement[14] of the tosylate by allylmagnesium chloride in a 1:1 THF/Et_2O mixture was far superior to protocols employing Cu catalysis: use of CuI,[15] CuBr·DMS,[16] or Li_2CuCl_4[17] together with the Grignard reagent gave complex mixtures and/or incomplete reactions. The use of stoichiometric copper reagents derived from allylzinc iodide by transmetalation with CuCN·2LiCl or CuBr·DMS also proved fruitless. Protection[18] of the lactam as the carbomethoxy derivative **6** then proceeded in excellent yield. The carbomethoxy species was chosen since (i) the protecting group would have to survive the strongly acidic conditions (methanol saturated with HCl) later required to cyclize **A5** via the corresponding iminium ion to the protected anatoxin-a **A4**,[10,11] (ii) it was expected to be easily cleaved in the final step, and (iii) this group enhances the electrophilicity of iminium ions.[11] The iminium ion precursor[12] was obtained by reduction of **6** with $NaBH_4$ in EtOH in the presence of H_2SO_4 followed by in situ ethanolysis.[11,19] The crude product obtained after aqueous workup and drying was then subjected to ozonolysis[11,20]

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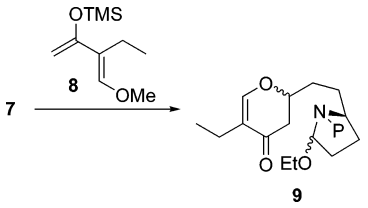
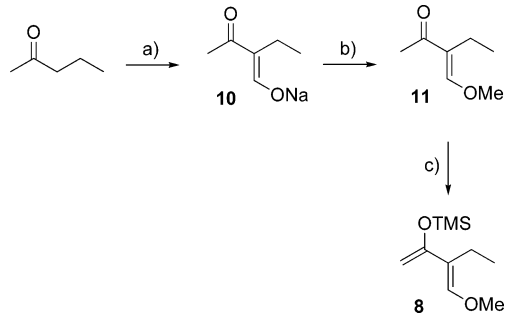
SCHEME 3. Hetero-Diels–Alder Reaction between Aldehyde 7 and Silyloxydiene 8, Yielding Pyranone 9[a]



[a] P = CO_2Me.

SCHEME 4[a]



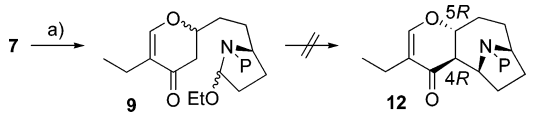
[a] Key: (a) (1) NaOMe (2.0 equiv), MeOCHO (2.5 equiv), Et_2O, 0 °C to rt, 50%; (b) AcCl, MeOH/*c*-hexane, 0 °C; then *p*-TsOH, MeOH/*c*-hexane, Δ, 43%; (c) TMSOTf, Et_3N, Et_2O, 0 °C, 72%.

followed by reductive workup yielding aldehyde **7** in 68% yield for the two steps as a 1:1 mixture of the two stereoisomers. Performing the reduction with $LiBH_4$[21] instead of $NaBH_4/H_2SO_4$ reduced the yield for the two steps to 43% overall. The synthesis of the key "branching point" aldehyde **7** was thus completed in five steps with 31% overall yield.

With the enantiopure aldehyde **7** in hand, the next key step was planned to be a stereoselective hetero-Diels–Alder reaction between **7** and silyloxydiene **8** yielding dihydropyrone **9** as shown in Scheme 3. It was our intention to control the absolute configuration at the new stereogenic center generated in the cycloaddition by use of a chiral catalyst[22] since we considered the stereocenter in the substrate to be too far removed from the site of reaction to provide useful levels of stereocontrol.

The synthesis of the requisite silyloxydiene **8**, derived from enone **11**, is shown in Scheme 4 and is based on modification of literature procedures.[23] Our method for preparation of **11**, 21% overall from 2-pentanone in a convenient reaction sequence, which avoids use of carcinogenic agents such as benzene and Me_2SO_4, is a considerable improvement over the previous route.[24] The synthesis of silyloxydiene **8** was completed by reaction of **11** with TMSOTf and Et_3N in 72% yield.[23f]

SCHEME 5[a]



[a] P = CO_2Me. Key: (a) **8**, (*S*)-(+)-BINOL, (*S*)-(+)-H_8-BINOL, $Ti(O^iPr)_4$, toluene, rt; then H_2SO_4, EtOH/THF, rt, 52%. The subsequent cyclization was unsuccessful.

For the following asymmetric hetero-Diels–Alder reaction of aldehyde **7** with silyloxydiene **8** we decided to use the catalyst system (*S*)-(+)-BINOL/(*S*)-(+)-H_8-BINOL/$Ti(O^iPr)_4$, since it was reported[22] to give excellent yields and stereoselectivity and uses commercially available ligands. The published method uses TFA in Et_2O to quench the reaction and generate the desired dihydropyrone system but since our product contains the acid-sensitive ethoxycarbamate functionality we opted to perform the quenching and generation of dihydropyrone with H_2SO_4 in EtOH/THF. In this way, the desired enone **9** was obtained in 52% yield as shown in Scheme 5.

We did not establish the absolute configuration of the new stereogenic center at this point, but only the 1:1 mixture of isomers of the ethoxycarbamate functionality could be seen on TLC and in NMR, indicating that the cycloaddition had proceeded with high stereoselectivity. Unfortunately, we were not able to cyclize the enone **9** to the protected pinnamine **12**. Attempts to perform the cyclization directly on **9** with $TiCl_4/CH_2Cl_2$/0 °C,[25] $TiCl_4/{}^iPr_2NEt/CH_2Cl_2$/0 °C,[26] $Sn(OTf)_2/{}^iPr_2NEt/CH_2Cl_2$/0 °C,[27] HCOOH/0 °C to rt,[28] TFA/0 °C to rt or HCl/MeOH/−50 to 0 °C[29] gave at best only rise to isolation of starting material and/or a crude product in which the ethoxycarbamate functionality had been exchanged for a hydroxycarbamate. The latter result implied that the iminium ion must have been generated, but still no cyclization occurred. We then attempted to synthesize the silyl enolate using previously described conditions TMSOTf/Et_3N/Et_2O, 0 °C[23f] but this resulted in a complex mixture. Attempts to generate the lithium enolate of the enone funcionality with LDA/THF/−78 °C also failed.

At this point, we decided to revise the route to pinnamine, while still wishing to take advantage of key intermediate **A3** (Scheme 6).

We envisioned that cyclization of the β-diketone **A7** onto an in situ generated iminium ion would be a plausible alternative to the unsuccessful enone/iminium ion cyclization. The subsequent reduction of the C-5 ketone (pinnamine numbering) would be expected to give the desired stereochemistry via reaction on the less hindered face of the molecule. For the synthesis of

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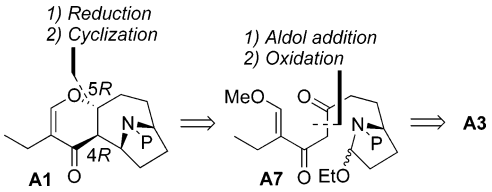
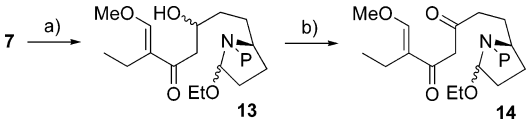
SCHEME 6. Revised Retrosynthesis of Protected Pinnamine A1 from Branching-Point Aldehyde A3



SCHEME 7[a]



[a] P = CO_2Me. Key: (a) **11**, $^iPr_2NH$, *n*-BuLi, THF, −78 °C, 87%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; then Et_3N, CH_2Cl_2, −78 to −10 °C, 78%.

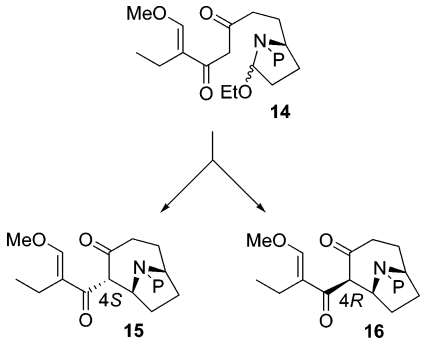
β-diketone **A7** we planned to use an aldol reaction between enone **11** and aldehyde **A3** followed by an oxidation (Scheme 6).

Thus, aldehyde **7** was reacted with the lithium enolate of **11** to give **13** as a mixture of two diastereomeric alcohols (Scheme 7).[30] The following oxidation to give β-diketone **14** proved rather troublesome. Whereas some commonly used methods such as TPAP/NMO/4Å MS/CH_2Cl_2/MeCN/rt, pyridine·SO_3/Et_3N/DMSO/rt,[31] and PCC/CH_2Cl_2/rt[32] resulted only in decomposition of starting material, use of Dess−Martin periodinane/CH_2Cl_2/rt seemed promising as judged by TLC of the reaction mixture. Unfortunately, and surprisingly, the product did not survive the conditions of workup (quenching with aqueous $Na_2S_2O_4$ followed by treatment with aqueous $NaHCO_3$). Swern oxidation,[33] however, proved to be the solution and initially the β-diketone **14** could be obtained in variable yields in the range of 39−58%. It was found that by allowing the reaction mixture to warm to no more than −10 °C and quenching with ice−water gave reproducible yields of around 78%. With the β-diketone **14** in hand, we were now ready to perform the key cyclization which could give rise to two products, the 4*S*-isomer **15** and the 4*R* isomer **16** (pinnamine numbering) as shown in Scheme 8.

Several different Lewis acids, bases, and solvents were screened on a small scale (up to ca. 0.1 mmol **14**), and it quickly became clear that even minor changes in solvent composition had a major impact on the product distribution. The results obtained are listed in Table 1. Characterization of the two products as the 4*S* or 4*R* isomer was not possible directly from NMR of the two compounds, but the absolute stereochemistry could be established at a later stage (vide infra).

Initially, much attention was devoted to performing the cyclization using $TiCl_4$ or (O^iPr)$TiCl_3$/$^iPr_2NEt$/CH_2Cl_2 at

SCHEME 8. Two Possible Products from Cyclization of 14 (Pinnamine Numbering)[a]



[a] P = CO_2Me.

−78 °C.[26,34] Although these conditions gave exclusively the 4*S*-isomer **15**, we were not able to obtain yields over 30% (entries 3 and 4). It was, however, using this system that the optimal quenching method was found. The products were found to be very sensitive to acidic and basic conditions and all products decomposed when quenching was performed by simply pouring the reaction mixture into water or adding a Et_3N/methanol mixture at −78 °C. Eventually, it was discovered that pouring the reaction mixture very slowly into a stirred saturated aqueous solution of $NaHCO_3$ caused the least amount of product loss, and this procedure remained our preferred method.

As can be seen in Table 1, use of $Sn(OTf)_2$[2,27] as Lewis acid quickly stood out as giving the highest yield and highest selectivity between the two possible cyclized isomers under different conditions. Thus, reaction of **14** with $Sn(OTf)_2$ (2.2 equiv) and *N*-ethylpiperidine (1.5 equiv) in THF at 0 °C gave, apart from starting material, exclusively the 4*S*-isomer **15** in 46% yield (entry 14), whereas when the reaction was performed in CH_2Cl_2 (entry 13) the 4*R*-isomer **16** was isolated in 32% yield along with traces of 4*S*-isomer **15**. We therefore decided to continue optimizing the reaction using $Sn(OTf)_2$ as Lewis acid, and the results are listed in Table 2.

As seen in Table 2, performing the reaction in CH_2Cl_2 (entries 7 and 8) required much lower temperatures, −78 to −35 °C, than when the reaction was performed in THF (entries 1−4) where temperatures below 0 °C resulted in a very slow reaction. For these solvents, warming the reaction mixture above −30 or 0 °C, respectively, resulted in decomposition (entry 3 vs 1 and entry 5 vs 7). Interestingly, use of the solvents CH_2Cl_2 (entries 7 and 8) and MeCN (entry 16) was optimized to give the 4*R*-isomer **16** as the major product (57−61% yield) and the 4*S*-isomer **15** as the minor product (21−24%), whereas THF (entry 1) as mentioned earlier gave the 4*S*-isomer **15** as the only product along with some starting material. Other solvents (entries 19−24) gave lower yields, so further work was concentrated on CH_2Cl_2, MeCN, and THF.

Since the 4*R*-isomer **16** could be obtained in relatively good yield (entries 7, 8, and 16) further optimization was concentrated on conditions leading selectively to the 4*S*-isomer **15**. Increasing the amount of base (entry 2) or

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TABLE 1. Obtained Results from Performing the Cyclization of 14 To Yield 4*S*-Isomer 15 and 4*R*-Isomer 16 (Pinnamine Numbering) under Different Conditions

entry	Lewis acid (equiv)	base (equiv)	solvent	*T* (°C) (time (h))	product composition
1[a]	TMSOTf (2.0)	$^{i}Pr_2NEt$ (1.0)	CH_2Cl_2	0 (1)	6% **15**
2[a]	$BF_3{\cdot}OEt_2$ (1.0)		CH_2Cl_2	0 (1)	complex mixture[c]
3[a]	$TiCl_4$ (1.1−5.0)	$^{i}Pr_2NEt$ (0−2.1)	CH_2Cl_2	−78 (1)	<30% **15**
4[a]	$(O^{i}Pr)TiCl_3$ (1.1)	$^{i}Pr_2NEt$ (1.1)	CH_2Cl_2	−78 (2)	<22% **15**
5[b]	$Cu(OTf)_2$ (2.2)	$^{i}Pr_2NEt$ (1.5)	CH_2Cl_2	0 to rt (3)	**16** major isomer; **14** major[c]
6[b]	$Cu(OAc)_2$ (2.3)	$^{i}Pr_2NEt$ (1.5)	CH_2Cl_2	0 to rt (3)	no reaction[c]
7[b]	$Sc(OTf)_3$ (1.2−2.4)	$^{i}Pr_2NEt$ (1.1)	CH_2Cl_2	0 (2)	**15/16** ca. 1:1; **14** major[c]
8[b]	$Sc(OTf)_3$ (1.2−2.4)	$^{i}Pr_2NEt$ (1.1−2.2)	THF	0 (3)	trace **15**[c]
9[a]	$AlCl_3$ (1.5)		CH_2Cl_2	−78 to 0 (2.5)	complex mixture[c]
10[a]	$SnCl_4$ (2.5)		CH_2Cl_2	−78 (1)	12% **15**
11[a]	$SnCl_4$ (2.1)	$^{i}Pr_2NEt$ (1.5)	THF	−30 to rt (3)	trace **15**[c]
12[a]	$ZnCl_2$ (2.0)	$^{i}Pr_2NEt$ (1.5)	THF/CH_2Cl_2	−78 to 0 (2)	no reaction[c]
13[a]	$Sn(OTf)_2$ (2.2)	*N*-ethylpiperidine (1.5)	CH_2Cl_2	0 (2)	32% **16**, trace **15**
14[a]	$Sn(OTf)_2$ (2.2)	*N*-ethylpiperidine (1.5)	THF	0 (3.5)	46% **15**

[a] 0.08−0.12 mmol **14** scale. [b] 0.05 mmol **14** scale. [c] As judged by TLC.

TABLE 2. $Sn(OTf)_2$-Mediated (2.2 equiv) Cyclization of 14 to 4*S*-Isomer 15 and 4*R*-Isomer 16 (Pinnamine Numbering) under Different Conditions

entry	base (equiv)	solvent	*T* (°C) (time (h))	**15** (4*S*)	**16** (4*R*)	**14**
1[a]	*N*-ethylpiperidine (1.5)	THF	0 (3.5)	46		NI[c]
2[a]	*N*-ethylpiperidine (2.1)	THF	0 (2.5)	38		NI[c]
3[a]	*N*-ethylpiperidine (1.5)	THF	rt to 30 (1.75)	29		45
4[a]	*n*-BuLi (1.1)	THF	−78 to rt (3.5)	NI[c]		NI[c] (major)
5[a]	*N*-ethylpiperidine (1.5)	CH_2Cl_2	0 (2)		33	
6[a]	*N*-ethylpiperidine (1.5)	CH_2Cl_2	−78 to −50 (2)	27	42	
7[a]	$^{i}Pr_2NEt$ (1.5)	CH_2Cl_2	−78 to −35 (2.5)	21	61	
8[b]	$^{i}Pr_2NEt$ (1.5)	CH_2Cl_2	−78 to −35 (2.5)	24	57	
9[a]	$^{i}Pr_2NEt$ (1.5)	CH_2Cl_2/THF 17:1	−35 to −30 (2 h)	30	36	24
10[a]	*N*-ethylpiperidine (1.5)	CH_2Cl_2/THF 9:1	0 (3.5)	48	NI[c]	NI[c]
11[b]	*N*-ethylpiperidine (1.5)	CH_2Cl_2/THF 9:1	0 (2.5)	41	19	20
12[a]	*N*-ethylpiperidine (1.5)	CH_2Cl_2/THF 3:1	0 (3.5)	53		NI[c]
13[b]	*N*-ethylpiperidine (1.5)	CH_2Cl_2/THF 3:1	0 (3.5)	36	trace	26
14[a]	*N*-ethylpiperidine (1.5)	CH_2Cl_2/THF 1:1	0 (3.5)	48		NI[c]
15[a]	*N*-ethylpiperidine (1.5)	CH_2Cl_2/THF 1:5	0 (3.5)	46		NI[c]
16[a]	$^{i}Pr_2NEt$ (1.5)	MeCN	0 (0.5)	24	58	
17[a]	$^{i}Pr_2NEt$ (1.5)	MeCN/THF 17:1	−35 to −30 (2)	26	56	NI[c]
18[a]	$^{i}Pr_2NEt$ (1.5)	MeCN/THF 9:1	−35 to −30 (2h)	28	29	15
19[a]	$^{i}Pr_2NEt$ (1.5)	Et_2O	0 (3.5)	trace		NI[c] (major)
20[a]	$^{i}Pr_2NEt$ (1.5)	DMF	0 to rt (8)			NI[c] (only)
21[a]	$^{i}Pr_2NEt$ (1.5)	NMP	0 to 60 (7)	trace	trace	NI[c] (major)
22[a]	$^{i}Pr_2NEt$ (1.5)	DME	0 (3)	34		49
23[a]	$^{i}Pr_2NEt$ (1.5)	dioxane	10 to rt (1.25)	21	6	26
24[a]	$^{i}Pr_2NEt$ (1.5)	toluene	−30 to 0 (2.5)	24	2	trace

[a] 0.10−0.12 mmol **14** scale. [b] 0.80 mmol **14** scale. [c] Not isolated.

changing the base to *n*-BuLi (entry 4) did not improve the yields. It was, however, found that using a CH_2Cl_2/THF mixture as solvent (entries 9−15)—and to a much lesser degree a MeCN/THF mixture (entries 17 and 18)—provided a useful way of controlling the selectivity of the reaction. Thus, on a small scale (0.10−0.12 mmol **14**) the optimal solvent composition was found to be CH_2Cl_2/THF 1:3 which gave 4*S*-isomer **15** in an improved 53% yield (entry 12). However, it was later found that a high content of THF in scaled-up reactions (0.80 mmol **14**) apparently had a detrimental effect on the yields due to product decomposition during quenching of the reaction (entry 13 vs 12). Therefore, we opted for a solvent composition with less THF, CH_2Cl_2/THF 1:9, which when scaled up gave the 4*S*-isomer **15** in an acceptable 41% yield along with 19% 4*R*-isomer **16** and 20% **14** (entry 11).

Subjecting **16** to conditions yielding **15** as the major product ($Sn(OTf)_2$ (2.2 equiv)/*N*-ethylpiperidine (1.5 equiv) in CH_2Cl_2/THF 1:9 at 0 °C) gave, apart from decomposition, almost complete epimerization to **15** but in only 31% yield. On the basis of the results presented above, we suggest that the cyclization reaction of **14** in THF (slower reaction) is under thermodynamic control, while the reaction in CH_2Cl_2 (faster reaction) is under kinetic control, although we have not performed experiments to verify this.

With the two isomers **15** and **16** now available, but still with undetermined stereochemistry at this point, the next step was the stereoselective reduction of the C-5 ketones (Scheme 9). Whereas attempts to use DIBALH[35] or $LiBH_4$ gave complex mixtures, the desired products could be obtained in good yields by reduction with $NaBH_4$ in CH_2Cl_2/EtOH 1:1 at 0 °C followed by quenching and cyclization with excess H_2SO_4. Interestingly, the reduction of **15** required 3 h whereas reduction of **16** was complete within 15 min. A crystalline product, **18**, was

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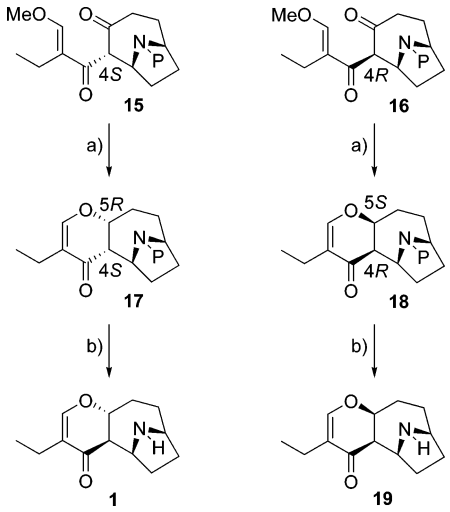
SCHEME 9[a]



[a] P = CO_2Me. Key: (a) $NaBH_4$, CH_2Cl_2/EtOH 1:1, 0 °C; then H_2SO_4, CH_2Cl_2/EtOH, −50 °C to rt, **15** → **17**: 70%, **16** → **18**: 63% (pinnamine numbering); (b) TMSI, MeCN, 0 °C to rt, **17** → **1**: 81%, **18** → **19**: 79%.

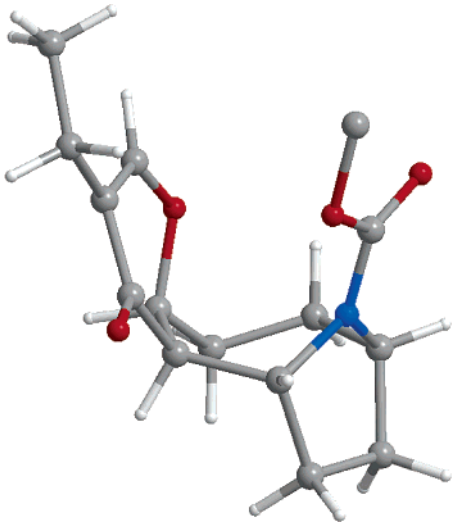
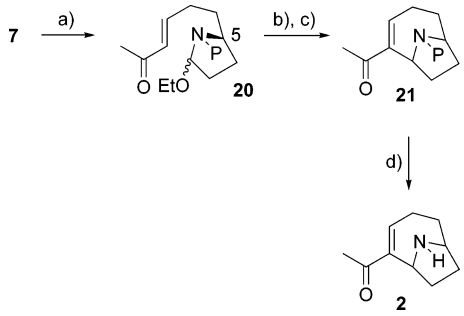


FIGURE 2. X-ray structure of **18**.

isolated after workup of the reaction of **16** and was assigned the 4*R*/5*S* configuration on the basis of NMR spectroscopy: H-4 signal: δ 2.48, 1H, dd, J = 5.8, 0.5 Hz, which corresponded well to expected values.[2] Final proof was obtained by X-ray crystallography (Figure 2).

This showed that reduction had occurred exclusively from the α face of **16**, an unexpected result which may be due to a conformational preference of the substrate induced by the exocyclic enone moiety. The other diketone isomer, **15**, must have the 4*S*-configuration, and the NMR spectrum of the product, **17**, obtained after reduction and cyclization showed the following H-4 signals, due to rotamers, δ 3.05 and 2.93, 0.48H and 0.52H, 2 × dd, J = 5.8, 5.8 Hz, which again corresponded well to expected values.[2] Since H-4 did not possess a coupling constant in the range 10.5−11.2 Hz which would be required if the product had the *trans*-configuration,[2] we have assigned the 4*S*/5*R*-*cis*-configuration to **17** (Scheme 9). Reduction of **15** had thus occurred, as expected, on

SCHEME 10[a]



[a] P = CO_2Me. Key: (a) $(MeO)_2P(=O)CH_2C(=O)CH_3$, $^iPr_2NEt$, LiCl, MeCN, rt, 88%; (b) HCl, MeOH, −50 °C to rt; (c), DBU, toluene, reflux, two steps, 51% overall; (d) TMSI, MeCN, 0 °C to rt, 65%.

the less-hindered β face of C-5, as required for pinnamine, but we were left with the problem of incorrect stereochemistry at C-4. Fortunately, it was found that complete epimerization at C-4 occurred during removal of the carbomethoxy protecting group with TMSI[36] giving pinnamine in 81% yield directly from **17**. The synthesis of enantiopure pinnamine thus comprises 10 steps from **3** in 4.8% overall yield, and our method of isolation (see the Experimental Section) provides the free amine as colorless crystals (mp = 47−51 °C). The trifluoroacetate salt of **1** (isolated as a yellowish oil) showed physical and spectral data in full accordance with those reported in the literature.[1a,2] Subjecting **18** to the same deprotection conditions as for pinnamine yielded 4*R*-5*S*-*epi*-pinnamine **19** in 78% yield (5.7% overall in 10 steps from **3**). In contrast to pinnamine, which appears to be a relatively stable substance, **19** decomposed rapidly even when kept at −20 °C, a fact which has so far precluded any biological testing of this compound.

With a successful route to pinnamine in hand via aldehyde **7**, we then turned our attention to the synthesis of anatoxin-a. As mentioned above, racemic **7** has been used previously for the synthesis[11] of racemic anatoxin-a, and we decided to simply adopt this method for the seemingly straightforward endgame expected to deliver the enantiomerically pure alkaloid. Thus, a Horner−Wadsworth−Emmons reaction[11,37] of aldehyde **7** with dimethyl (2-oxopropyl)phosphonate under Masamune-Roush conditions gave the desired enone **20** in excellent yield (Scheme 10). Cyclization of **20** (which was a single stereoisomer at C-5) in methanol saturated with HCl followed by refluxing the crude product mixture in the presence of DBU yielded **21** in 51% yield.[11,37b] At this point, however, we were unpleasantly surprised to find that the product was completely racemic, a result which was reproducible using different batches of **20**. This was all the more unexpected in view of an earlier report[10] describing an identical reaction sequence leading to enantiopure product from the *N*-tosyl analogue of **20** (with a methoxy rather than an ethoxy group in the α-position). Other related cyclizations[29] have also been

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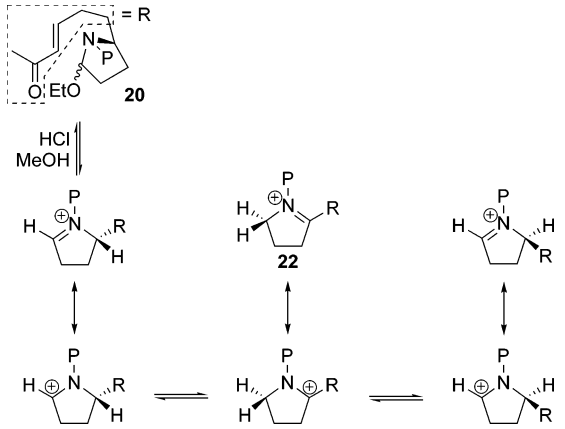
SCHEME 11. Proposed Mechanism for Racemization during Cyclization of Enantiopure 20 To Yield Racemic 21[a]



[a] P = CO_2Me.

reported to occur without loss of enantiopurity, in sharp contrast to the present results. While we have no good explanation for these discrepancies, we propose that the racemization occurring in our hands goes via hydride abstraction by the iminium ion as shown in Scheme 11, and we note that Tietze[38] has recently made similar observations regarding iminium ion-induced 1,5-hydride shifts. (We did not observe any spirocyclic products which could be expected from cyclization of the presumably much less reactive[39] iminium ion **22**, Scheme 11.)

Other attempts at performing the cyclization of **20** with H_2SO_4/MeOH/60 °C,[37b] TFA/CH_2Cl_2/rt,[40] $TiCl_4$/CH_2Cl_2/−78 °C,[41] DMAP/$Sn(OTf)_2$/CH_2Cl_2/0 °C to rt, or *p*-TsOH/benzene/reflux did not give any useful results. The synthesis of racemic anatoxin-a **2** was completed by deprotection (TMSI[36]) in 65% yield (9% overall for nine steps).

Conclusion

We have demonstrated the total synthesis of enantiopure pinnamine **1** in 10 steps and 4.8% overall yield from the commercially available pyroglutamic acid derivative **3**. The present route is six steps shorter than the only previously reported synthesis,[2] and our methodology also provides, via a stereochemically divergent cyclization/reduction sequence, an entry to the nonnatural congener **19** (5.7% overall yield for 10 steps). Enantiopure aldehyde **7**, a key intermediate in the pinnamine synthesis, could also be used for the total synthesis of anatoxin-a **2** (9% overall for nine steps). However, in complete contrast to literature precedent, the iminium ion-induced cyclization reaction in the anatoxin-a endgame gave rise to complete racemization, and the present unexpected results may serve as a caveat.

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Experimental Section

(*S*)-5-(Toluene-4-sulfonyloxymethyl)pyrrolidin-2-one (4). To a solution of **3** (5.00 g, 43.3 mmol) and TsCl (10.0 g, 52.5 mmol) in CH_2Cl_2 (160 mL) at rt under N_2 were added Et_3N (12.0 mL, 86.1 mmol) and DMAP (531 mg, 4.35 mmol). The mixture was then stirred for 20 h at rt. The reaction mixture was diluted with CH_2Cl_2 (100 mL), poured into water (250 mL), and acidified with concd HCl (3.0 mL). The organic phase was isolated, the aqueous phase was extracted with CH_2Cl_2 (2 × 75 mL), and the combined organic phases were dried over $MgSO_4$ and filtered. Silica gel (13.5 g) was added to the filtrate, and the suspension was concentrated and dried in vacuo. The silica gel mixture was added to the top of a short silica gel column and the product was passed through using EtOAc/MeOH 20:1 as eluent, yielding **4** (11.5 g, 98%) as a colorless solid: R_f (EtOAc/MeOH 20:1) = 0.34; mp = 128−130 °C (lit.[13] mp = 125−126 °C); $[\alpha]^{20}_D$ 20.3 (*c* 0.99, $CHCl_3$) (lit.[13b] $[\alpha]^{20}_D$ 20.4 (*c* 1.05, $CHCl_3$)); ^1H and ^{13}C NMR and IR spectra were in full accordance with those reported in the literature.[13] Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20; S, 11.91. Found: C, 53.26; H, 5.52; N, 5.24; S, 11.69.

(*S*)-5-(But-3-enyl)pyrrolidin-2-one (5). To a suspension of **4** (10.8 g, 40.1 mmol) in Et_2O/THF 5:3 (400 mL) at 0 °C under N_2 was added 2 M allylmagnesium chloride in THF (100 mL, 200 mmol) over 25 min. Stirring was then continued for 5 h at rt. The reaction mixture was poured into satd NH_4Cl (500 mL), and CH_2Cl_2 (1000 mL) was added. The organic phase was isolated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 500 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (CH_2Cl_2/MeOH 20:1) of the residue yielded impure **5** (4.33 g) as a yellow-orange oil. Flash chromatography (EtOAc/MeOH 20:1) of the isolated oil yielded pure **5** (2.86 g, 51%) as a pale yellowish oil: R_f (CH_2Cl_2/MeOH 20:1) = 0.31; R_f (EtOAc/MeOH 20:1) = 0.31; $[\alpha]^{20}_D$ 14.5 (*c* 1.00, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (1H, br s), 5.80 (1H, dddd, J = 17.0, 10.2, 6.8 Hz), 5.06 (1H, m, J = 17.0 Hz), 5.00 (1H, m, J = 10.2 Hz), 3.65 (1H, dddd), 2.42−2.19 (3H, m), 2.12 (2H, m), 1.81−1.50 (3H, m); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 178.5 (C), 137.4 (CH), 115.3 (CH_2), 54.1 (CH), 35.7 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 27.1 (CH_2); IR (neat) 3203 (s), 3089 (s), 1698 (s), 1641 (m). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.81; H, 9.28; N, 9.97.

(*S*)-2-But-3-enyl-5-oxopyrrolidine-1-carboxylic Acid Methyl Ester (6). To a solution of **5** (2.50 g, 18.0 mmol) in THF (80 mL) under N_2 at −78 °C was added dropwise 1.6 M *n*-BuLi in hexanes (11.8 mL, 18.9 mmol) over 10 min. Stirring was continued for 1 h at −78 °C whereupon freshly distilled methyl chloroformate (1.47 mL, 21.6 mmol) was added, and the reaction mixture was allowed to heat slowly to 0 °C over 2.5 h. The reaction mixture was poured into satd aq NH_4Cl (70 mL), and the mixture was extracted with EtOAc (3 × 90 mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated, and dried in vacuo. Flash chromatography of the residue yielded **6** (3.21 g, 91%) as a pale yellowish oil: R_f (EtOAc/heptane 1:1) = 0.35; $[\alpha]^{20}_D$ −87.3 (*c* 1.04, EtOH); ^1H NMR (300 MHz, $CDCl_3$): δ 5.74 (1H, dddd, J = 16.9, 10.1, 6.5 Hz), 4.99 (1H, m, J = 16.9 Hz), 4.94 (1H, m, J = 10.2 Hz), 4.14 (1H, m), 3.79 (3H, s), 2.56 (1H, ddd, J = 17.8, 11.1, 9.1 Hz), 2.39 (1H, ddd, J = 17.8, 9.4, 2.7 Hz), 2.15−1.70 (5H, m), 1.59−1.45 (1H, m); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 173.8 (C), 152.1 (C), 137.0 (CH), 115.3 (CH_2), 57.6 (CH), 53.4 (CH_3), 32.2 (CH_2), 31.2 (CH_2), 29.6 (CH_2), 22.3 (CH_2); IR (neat): 3076 (m), 1792 (s), 1750 (s), 1717 (s), 1641 (m). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.07; H, 7.64; N, 7.14.

2-Ethoxy-5-(*S*)-(3-oxopropyl)pyrrolidine-1-carboxylic Acid Methyl Ester (7). To a solution of **6** (1.48 g, 7.50 mmol) in EtOH (60 mL) at −20 °C (drying tube fitted to flask) were added $NaBH_4$ (851 mg, 22.5 mmol) and 5 drops of 1 M H_2SO_4 in EtOH. During 6.5 h, 5 drops of 1 M H_2SO_4 in EtOH were added every 15 min. 1M H_2SO_4 in EtOH (14.5 mL) was

then added dropwise until the excess of $NaBH_4$ had been destroyed and pH ~ 3. The mixture was stirred for 1.5 h at 0−2 °C and then poured into satd $NaHCO_3$ (75 mL) and diluted with water (45 mL). The mixture was extracted with CH_2Cl_2 (3 × 120 mL), and the combined organic phases were washed with brine (60 mL), dried over Na_2SO_4, filtered, concentrated, and dried in vacuo yielding the crude product (1.59 g) as a colorless oil. The crude product was dissolved in CH_2Cl_2 (75 mL) under N_2, the solution was cooled to −78 °C, and O_2 was bubbled through for a short time. O_3 was then bubbled through during 20 min until the reaction mixture remained blue for a few minutes. PPh_3 (2.16 mg, 8.24 mmol) was added, and the reaction mixture was allowed to warm to rt overnight while stirring under N_2. The mixture was concentrated and dried in vacuo, and flash chromatography of the residue yielded **7** (1.17 g, 68%) as a colorless oil: R_f (heptane/EtOAc 3:2) = 0.30; $[\alpha]^{20}_D$ −41.3 (*c* 1.03, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (1H, s), 5.45−5.20 (1H, m,), 3.98−3.79 (1H, m), 3.71 (3H, s), 3.66−3.37 (2H, m), 2.52−2.42 (2H, m), 2.24−1.60 (6H, m), 1.17 (3H, t, J = 7.1 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 202.0 (CH), 156.5/155.8 (C), 88.4/87.8 (CH), 62.9/62.5 (CH_2), 57.5/56.8, (CH), 52.4 (CH_3), 39.9 (CH_2), 32.1/31.7 (CH_2), 28.9/28.2 (CH_2), 27.7 (CH_2), 15.0 (CH_3); IR (neat) 2725 (m), 1706 (s). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.41; H, 8.23; N, 6.02.

2-Ethyl-3-oxobutanal Sodium Salt (10). To a well-stirred suspension of NaOMe[23c] (10.1 g, 187 mmol) in Et_2O (80 mL) under N_2 at 0 °C was added methyl formate (14.5 mL, 235 mmol) giving a thick suspension. 2-Pentanone (10.0 mL, 93.6 mmol) was then added dropwise over a period of 15 min. The mixture was allowed to heat to rt, and stirring was continued for 4.5 h. The precipitate was filtered off and dried in vacuo, yielding crude **10** (6.34 g, 50%) as a pale yellow solid which was used in the ensuing reaction without further purification: ^{1}H NMR (300 MHz, D_2O) δ 8.88 (0.83H, s), 8.38 (0.17H, s), 2.10 (3H, s) 2.06 (2H, q, J = 7.5 Hz), 0.77 (3H, t, J = 7.5 Hz); ^{13}C NMR (75.4 MHz, D_2O) δ 198.0, 182.4, 171.2, 121.0, 22.4, 15.2, 13.5.

(*E*)-3-(Methoxymethylene)pentan-2-one (11). Acetyl chloride (3.65 mL, 51.3 mmol) was added dropwise to MeOH (17.5 mL) at 0 °C, and the mixture was stirred for a few minutes. The mixture was poured slowly into a suspension of the crude sodium salt **10** (6.34 g, 46.6 mmol) in *c*-hexane (45 mL) and stirring was continued for 30 min at 0 °C. The mixture was then filtered into a 100 mL flask, rinsing the flask with *c*-hexane (20 mL). *p*-TSA monohydrate (175 mg, 0.92 mmol) was added to the resulting biphasic system, and the flask was fitted with a 15 cm Vigreux column. The solvents were then distilled off (over ca. 25 min) until ca. 55 mL distillate had been collected and the distilling temperature had risen to ca. 81 °C. *c*-hexane/MeOH 2:1 (9 mL) was then added to the reaction mixture, and further ca. 10 mL distillate was distilled off (over ca. 10 min) until the distilling temperature had again risen to ca. 81 °C. This was repeated one further time, continuing the distillation until ca. 25 mL distillate had been collected, thus concentrating the mixture volume to ca. 10 mL. The mixture was then allowed to cool to rt, and short column flash chromatography of the residue gave, after careful concentration at rt, the pure product containing traces of Et_2O. Flask to flask distillation in vacuo yielded pure **11** (2.56 g, 43%) as a pale yellowish oil: R_f (Et_2O/pentane 1:1) = 0.28. bp = 80−81 °C/14 mmHg (lit.[24] bp = 70−73 °C/13 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (1H, s), 3.86 (3H, s), 2.25 (2H, q, J = 7.4 Hz), 2.20 (3H, s), 0.93 (3H, t, J = 7.4 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 196.7 (C), 160.2 (CH), 124.0 (C), 61.3 (CH_3), 25.2 (CH_3), 16.1 (CH_2), 13.1 (CH_3); IR (neat) 1635 (s). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.35; H, 9.25.

((*E*)-3-(Methoxymethylene)pent-1-en-2-yloxy)trimethylsilane (8). To a solution of **11** (2.38 g, 18.6 mmol) and Et_3N (3.40 mL, 24.4 mmol) in Et_2O (20 mL) at 0 °C under N_2 was added TMSOTf (3.50 mL, 19.3 mmol) dropwise over 10 min. Stirring was continued for 45 min at 0 °C during which time an oily red-orange lower phase was formed. The reaction mixture was then transferred to a separatory funnel, and the red-orange lower oily phase was separated and discarded. The organic phase was washed with 1.0 M aqueous $NaHCO_3$ (10 mL), and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Fractional distillation of the residue through a 150-mm Vigreux column gave **8** (2.66 g, 72%) as a colorless oil: bp = 79−84 °C/14 mmHg (lit.[24] bp = 72−73 °C/15 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (1H, s), 4.29 (1H, d, J = 1.2 Hz), 4.15 (1H, d, J = 1.2 Hz), 3.67 (3H, s), 2.19 (2H, q, J = 7.5 Hz), 1.00 (3H, t, J = 7.5 Hz), 0.22 (9H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 154.7 (C), 118.1 (C), 146.6 (CH), 89.2 (CH_2), 60.1 (CH_3), 18.0 (CH_2), 13.4 (CH_3), 0.1 (3 × CH_3); IR (neat) 3124 (m), 3052 (m), 1648 (s), 1593 (m). Anal. Calcd for $C_{10}H_{20}O_2Si$: C, 59.95; H, 10.06. Found: C, 59.99; H, 9.92.

Dihydropyrone (9). To solution of (*S*)-BINOL (23.0 mg, 0.080 mmol), (*S*)-H_8-BINOL (24.0 mg, 0.082 mmol) and $Ti(O^iPr)_4$ (0.024 mL, 0.081 mmol) in toluene (0.20 mL) under N_2 at rt was added **7** (367 mg, 1.60 mmol) under N_2 at rt. Freshly distilled **8** (481 mg, 2.40 mmol) was then added, and the reaction mixture was stirred at rt for 41 h. THF (6.0 mL) and EtOH (6.0 mL) were added followed by EtOH/H_2SO_4 1:1 (0.38 mL, 3.56 mmol H_2SO_4), and the mixture was stirred for 1 h at rt. The mixture was poured into satd $NaHCO_3$ (10 mL), and the resulting mixture was diluted with water (6 mL). The mixture was then extracted with EtOAc (3 × 20 mL), and the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered, concentrated, and dried in vacuo. Flash chromatography of the residue yielded **9** (272 mg, 52%) as a yellowish oil: R_f (heptane/EtOAc 3:2) = 0.31; $[\alpha]^{20}_D$ −19.6 (*c* 0.76, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (1H, s), 5.45−5.20 (1H, m), 4.40−4.26 (1H, m), 3.97−3.76 (1H, m), 3.71 (3H, s), 3.67−3.35 (2H, m), 2.56−2.37 (2H, m), 2.27−1.46 (10H, m), 1.17 (3H, t, J = 7.0 Hz), 1.01 (3H, t, J = 7.5 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 192.6 (C), 159.4 (CH), 156.5/155.7 (C), 119.5 (C), 88.3/87.7 (CH), 79.0 (CH), 62.9/62.4 (CH_2), 57.8/57.3 (CH), 52.4 (CH_3), 41.8/41.7 (CH_2), 32.3/31.8 (CH_2), 31.0/30.8 (CH_2), 30.3 (CH_2), 29.1/28.3 (CH_2), 18.5 (CH_2), 15.1 (CH_3), 13.7 (CH_3); IR (neat) 1702 (s), 1671 (s), 1618 (s). Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36; N, 4.30. Found: C, 62.97; H, 8.21; N, 4.15.

2-Ethoxy-5-(*S*)-((*E*)-3-hydroxy-6-(methoxymethylene)-5-oxooctyl)pyrrolidine-1-carboxylic Acid Methyl Ester (13). ^{i}Pr$_2$NH (0.80 mL, 5.71 mmol) was dissolved in THF (3.0 mL) under N_2, and the mixture was cooled to −78 °C. *n*-BuLi (1.60 M) in hexanes (3.55 mL, 5.68 mmol) was added dropwise, and the mixture was stirred for 30 min at −78 °C. A solution of **11** (692 mg, 5.40 mmol) in THF (5.0 mL) was added dropwise, and the mixture was stirred for 1 h further at −78 °C. A solution of **7** (1.03 g, 4.50 mmol) in THF (3.0 mL) was then added, and stirring was continued for 1.5 h at −78 °C. The reaction mixture was then poured into brine (30 mL) and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated (at rt), and dried in vacuo. Flash chromatography of the residue yielded **13** (1.40 g, 87%) as a colorless oil: R_f (Et_2O) = 0.28; $[\alpha]^{20}_D$ −34.8 (*c* 1.03, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.17 (1H, br s), 5.44−5.19 (1H, m), 4.13−3.99 (1H, m), 3.89/3.89 (3H, 2 × s), 3.70/3.69 (3H, 2 × s), 3.92−3.76 (1H, m), 3.67−3.38 (2H, m), 2.90−2.64 (1H, m), 2.63−2.41 (1H, m), 2.24 (2H, q, J = 7.5 Hz), 2.16−1.32 (8H, m), 1.16 (3H, t, J = 7.0 Hz), 0.93 (3H, t, J = 7.5 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 199.6 (C), 161.0/160.8 (CH), 156.8/155.7 (C), 123.8 (C), 88.2/87.7 (CH), 68.1 (CH), 62.6/62.3 (CH_2), 61.5 (CH_3), 52.2 (CH_3), 58.2/57.8 (CH), 43.0/42.3 (CH_2), 32.5 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 31.7 (CH_2), 31.4 (CH_2), 29.2 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 16.0 (CH_2), 15.0 (CH_3), 13.1 (CH_3); IR (neat) 3473 (m), 1697 (s), 1628 (s). Anal. Calcd for $C_{18}H_{31}NO_6$: C, 60.40; H, 8.74; N, 3.92. Found: C, 60.70; H, 8.95; N, 3.65.

2-Ethoxy-5-(*S*)-((*E*)-6-(methoxymethylene)-3,5-dioxooctyl)pyrrolidine-1-carboxylic Acid Methyl Ester (14). To a solution of DMSO (0.64 mL, 9.02 mmol) in CH_2Cl_2 (10.0 mL) under N_2 at −50 °C was added dropwise oxalyl chloride (0.39 mL, 4.47 mmol). After 5 min, the temperature was cooled to −78 °C, and a solution of **13** (1.25 g, 3.50 mmol) in CH_2Cl_2 (20.0 mL) was added over 5 min and stirring was continued for 1.5 h. Et_3N (2.45 mL, 17.6 mmol) was then added, and the mixture was allowed to heat to −10 °C over 2 h. The reaction mixture was poured into ice−water (25 mL ice-cold water + 10 g ice), and the organic phase was isolated. The aqueous phase was extracted with CH_2Cl_2 (2 × 35 mL), and the combined organic phases were washed with brine (2 × 15 mL), dried over Na_2SO_4, filtered, concentrated (at rt), and dried in vacuo. Flash chromatography of the residue yielded **14** (974 mg, 78%) as a yellowish oil: R_f (heptane/EtOAc 3:2) = 0.30; $[\alpha]^{20}_D$ −20.5 (*c* 1.01, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.22 (1H, br s), 5.75−5.54 (1H, m), 5.44−5.20 (1H, m), 3.90/3.84 (3H, 2 × s), 3.71/3.70 (3H, 2 × s), 3.96−3.76 (1H, m), 3.75−3.35 (2H, m), 2.62−1.59 (10H, m), 1.24 and 1.17 (0.42H and 2.58H, 2 × t, J = 7.0 Hz), 1.00 and 0.92 (1.96H and 1.04H, 2 × t, J = 7.5 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 204.7 (C), 195.0/193.1 (C), 185.0/183.5 (C), 156.5/155.7 (C), 124.0 (C), 117.7/116.9 (C), 162.7 (CH), 156.5 (CH), 94.6 (CH), 88.3/87.8 (CH), 62.8/62.4 (CH_2), 61.7/61.3 (CH_3), 52.4 (CH_3), 57.8/57.2 (CH), 53.7 (CH_2), 39.0 (CH_2), 35.2 (CH_2), 35.0 (CH_2), 32.2 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 28.3 (CH_2), 16.5/16.2 (CH_2), 15.1 (CH_3), 13.4/13.0 (CH_3); IR (neat) 1699 (s), 1635 (s). Anal. Calcd for $C_{18}H_{29}NO_6$: C, 60.83; H, 8.22; N, 3.94. Found: C, 60.89; H, 8.39; N, 3.92.

2-(*S*)-((*E*)-2-(Methoxymethylene)butan-1-oyl)-9-azabicyclo[4.2.1]non-2-ene-9-carboxylic Acid Methyl Ester (15). To a solution of $Sn(OTf)_2$ (733 mg, 1.76 mmol) in THF/CH_2Cl_2 1:9 (8.0 mL) at 0 °C under N_2 was added *N*-ethylpiperidine (0.17 mL, 1.23 mmol), and stirring was continued for 5 min. A solution of **14** (285 mg, 0.80 mmol) in THF/CH_2Cl_2 1:9 (3.5 mL) was then added dropwise, and stirring was continued for 2.5 h at 0 °C. The reaction mixture was then poured dropwise into vigorously stirred satd aq $NaHCO_3$ (15 mL) at 0 °C, and stirring was continued for a few minutes. The mixture was then diluted with cold water (20 mL) and CH_2Cl_2 (30 mL), and the organic phase was isolated. The aqueous phase was extracted with CH_2Cl_2 (4 × 30 mL), and the combined organic phases were dried over Na_2SO_4, filtered, concentrated (at rt), and dried in vacuo. Flash chromatography of the residue yielded **15** (101 mg, 41%) as a colorless solid. Also isolated were **16** (47 mg, 19%) and **14** (57 mg, 20%): R_f (heptane/EtOAc 1:1) = 0.37; mp = 92−96 °C; $[\alpha]^{20}_D$ −152.7 (*c* 0.59, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 and 7.20 (0.73H and 0.27H, 2 × s), 4.57−4.39 (2H, m), 4.37−4.29 (1H, m), 3.93 (3H, 2 × s), 4.74/4.69 (3H, 2 × s), 2.99 (1H, ddd, J = 13.0, 13.0, 4.4 Hz), 2.55 (1H, ddd, J = 13.0, 4.0, 4.0 Hz), 2.34−1.65 (8H, m), 0.90 (3H, t, J = 7.5 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 209.3/209.3 (C), 195.6/195.4 (C), 162.1/161.5 (CH), 154.0/153.2 (C), 123.8 (C), 63.5/62.2 (CH), 56.1/55.9 (CH), 55.1/54.5 (CH), 62.0/61.9 (CH_3), 52.8/52.6 (CH_3), 40.6/40.5 (CH_2), 33.2/32.3 (CH_2), 29.4/28.6 (CH_2), 26.1/25.0 (CH_2), 16.2/16.1 (CH_2), 13.0 (CH_3); IR (KBr) 1701 (s), 1623 (s). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.88; H, 7.56; N, 4.48.

4-(*R*)-((*E*)-2-(methoxymethylene)butan-1-oyl)-9-azabicyclo[4.2.1]non-2-ene-9-carboxylic Acid Methyl Ester (16). To a suspension of $Sn(OTf)_2$ (733 mg, 1.759 mmol) in CH_2Cl_2 (8.0 mL) at 0 °C under N_2 was added ^{i}Pr$_2$NEt (0.205 mL, 1.198 mmol), and stirring was continued for 5 min. The mixture was then cooled to −78 °C, and a solution of **73** (285 mg, 0.802 mmol) in CH_2Cl_2 (3.5 mL) was then added dropwise. The reaction mixture was then allowed to heat to −30 °C over 1.5 h, and stirring was continued at −30 to −35 °C for a further 30 min. The reaction mixture was then poured slowly into satd aq $NaHCO_3$ (15 mL) at 0 °C, and stirring was continued for a few minutes. The mixture was diluted with water (20 mL) and CH_2Cl_2 (30 mL), and the organic phase was isolated. The aqueous phase was extracted with CH_2Cl_2 (4 × 30 mL), and the combined organic phases were dried over Na_2SO_4, filtered, concentrated, and dried in vacuo. Flash chromatography of the residue yielded **16** (141 mg, 57%) as a colorless oil. Also isolated was **15** (59 mg, 24%). **16**: R_f (heptane/EtOAc 1:2) = 0.32; $[\alpha]^{20}_D$ −49.4 (*c* 0.50, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19/7.14 (1H, 2 × s), 4.76−4.38 (2H, m), 3.88/3.83 (4H, 2 × s), 4.70/4.65 (3H, 2 × s), 3.26−3.05 (1H, m), 2.47−1.94 (6H, m), 1.76−1.40 (3H, m), 0.93 (3H, t, J = 7.5 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 209.7/209.5 (C), 193.4 (C), 160.6/160.1 (CH), 154.7 (C), 123.5/123.2 (C), 67.1/66.8 (CH), 55.4 (CH), 54.8 (CH), 61.6 (CH_3), 52.4 (CH_3), 38.8/38.4 (CH_2), 31.4/30.7 (CH_2), 30.6/30.0 (CH_2), 29.0/28.4 (CH_2), 16.7 (CH_2), 13.0 (CH_3); IR (KBr) 1700 (s), 1628 (s); Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.87; H, 7.27; N, 4.54.

4*S*,5*R*-*epi*-Pinnamine-*N*-carboxylic Acid Methyl Ester (17). To a solution of **15** (124 mg, 0.401 mmol) in EtOH/CH_2Cl_2 1:1 (14 mL) at 0 °C in a 25 mL flask fitted with a drying tube was added $NaBH_4$ (45 mg, 1.190 mmol), and stirring was continued at 0 °C for 3 h. The mixture was cooled to −50 °C, 1 M H_2SO_4 in EtOH (1.50 mL, 1.50 mmol H_2SO_4) was added dropwise, and stirring was continued for 45 min at rt after bubbling had ceased. The mixture was then poured into satd $NaHCO_3$ (15 mL), and the mixture was diluted with water (10 mL). The mixture was then extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered, concentrated, and dried in vacuo. Flash chromatography of the residue yielded **17** (78 mg, 70%) as a colorless oil: R_f (heptane/EtOAc 2:1) = 0.22; $[\alpha]^{20}_D$ 114.2 (*c* 0.50, EtOH); ^{1}H NMR (300 MHz, MeOD) δ 7.49/7.48 (1H, 2 × s), 4.72−4.62 (1H, m), 4.54−4.42 (1H, m), 4.34−4.24 (1H, m), 3.73/3.70 (3H, 2 × s), 3.05 and 2.93 (0.48H and 0.52H, 2 × dd, J = 5.8, 5.8 Hz, C(=O)C*H*), 2.30−2.04 (5H, m), 2.00−1.58 (5H, m), 1.02 (3H, t, J = 7.4 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 194.8 (C), 162.8/162.6 (CH), 156.2 (C), 122.2 (C), 81.5 (CH), 58.9/58.6 (CH), 55.7/55.6 (CH), 53.3/53.2 (CH_3), 52.3/51.2 (CH), 33.5/32.9 (CH_2), 31.3/30.6 (CH_2), 28.2/28.0 (CH_2), 26.8/26.2 (CH_2), 19.6 (CH_2), 14.4 (CH_3); IR (neat) 1698 (s), 1662 (s), 1610 (s). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.55; H, 7.39; N, 4.84.

4*R*,5*S*-*epi*-Pinnamine-*N*-carboxylic Acid Methyl Ester (18). To a solution of **16** (108 mg, 0.349 mmol) in EtOH/CH_2Cl_2 1:1 (12 mL) at 0 °C in a 25 mL flask fitted with a drying tube was added $NaBH_4$ (20 mg, 0.529 mmol), and stirring was continued at 0 °C for 15 min. The mixture was cooled to −50 °C, 1 M H_2SO_4 in EtOH (0.66 mL, 0.66 mmol H_2SO_4) was then added dropwise, and stirring was continued for 30 min at rt after bubbling had ceased. The mixture was then poured into satd $NaHCO_3$ (15 mL), and the mixture was diluted with water (10 mL). The mixture was then extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered, concentrated, and dried in vacuo. Flash chromatography of the residue yielded **18** (61 mg, 63%) as a colorless solid: R_f (heptane/EtOAc 1:2) = 0.40; mp = 96.5−98.5 °C; $[\alpha]^{20}_D$ −103.6 (*c* 0.55, EtOH); ^{1}H NMR (300 MHz, MeOD) δ 7.38 and 7.28 (0.74H and 0.26H, 2 × s), 4.83−4.74 (1H, m), 4.46−4.31 (2H, m), 3.61 and 3.48 (0.80H and 2.20H, 2 × s), 2.48 (1H, dd, J = 5.8, 0.5 Hz, C(=O)C*H*), 2.51−1.72 (9H, m), 1.60−1.48 (1H, m), 1.03/1.02 (3H, 2 × t, J = 7.5 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 196.9/196.5 (C), 162.5/162.1 (CH), 156.1/155.8 (C), 120.4/119.9 (C), 80.6 (CH), 59.2 (CH), 59.1 (CH), 58.8 (CH), 58.0/57.6 (CH), 53.0/52.5 (CH_3), 35.4/34.7 (CH_2), 29.3/28.7 (CH_2), 28.4/27.8 (CH_2), 27.0/26.9 (CH_2), 19.9 (CH_2), 14.1/14.0 (CH_3); IR (KBr) 1702 (s), 1649 (s), 1617 (s). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.58; H, 7.65; N, 4.96.

Crystal data: **18**, M = 279.33, orthorhombic, a = 7.3144(5) Å, b = 8.3260(6) Å, c = 23.5690(17) Å, V = 1435.34(18) Å^3, T = 200(2) K, space group $P2_12_12_1$, Z = 4, D_x = 1.293 g cm^{-3}, crystal size = 0.24 × 0.15 × 0.08 mm^3, μ(Mo Kα) = 0.093 mm^{-1}, 10266 reflections measured, 3449 unique (R_{int} = 0.0255)

and 3006 reflections with $I > 2\sigma(I)$ wich were used in all calculations. The final R1 was 0.0597 (observed data) and wR(F^2) was 0.1537 (all data). The Flack x parameter is 0.3(15).

General Procedure for Deprotection of Carbomethoxy Amides. To a solution of the carbomethoxy amide in (0.098 mmol) in MeCN (0.60 mL) under N_2 at 0 °C was added TMSI (0.0175 mL, 0.129 mmol), and the mixture was allowed to heat to rt slowly overnight (stirred for 17−19 h). MeOH (0.50 mL) was added, and stirring was continued for 10 min at rt. The mixture was then concentrated and dried in vacuo. Flash chromatography of the residue yielded the free amine.

Pinnamine (1). Deprotection of **17** (27.5 mg, 0.098 mmol) following the general procedure yielded the free amine **1** (17.6 mg, 81%) as a colorless solid: R_f (CH_2Cl_2/MeOH/Et_3N 20:1:0.1) = 0.15; mp = 47−51 °C; $[\alpha]^{20}_D$ 116.7 (*c* 0.63, MeOH); ^{1}H NMR (300 MHz, MeOD) δ 7.34 (1H, s, C=C*H*), 4.48 (1H, dd, J = 10.0, 1.3 Hz, C(=O)CHC*H*N), 4.30 (1H, m, J = 13.5 Hz, C(=O)CHC*H*O), 3.55 (1H, dddd, J = 8.1, 3.3, 3.3, 0.7 Hz, NC*H*), 2.28 (1H, d, J = 13.5 Hz, C(=O)C*H*), 2.28−1.56 (10H, m), 1.01 (3H, t, J = 7.5 Hz, CCH_2CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 195.9 (C), 161.4 (CH), 120.4 (C), 83.4 (CH), 59.1 (CH), 59.0 (CH), 52.2 (CH), 35.8 (CH_2), 33.4 (CH_2), 30.9 (CH_2), 30.0 (CH_2), 19.9 (CH_2), 14.5 (CH_3); IR (KBr) 1669 (s), 1616 (s); HRMS (FAB$^+$) calcd for $C_{13}H_{20}NO_2$ [M + H]$^+$ *m/z* 222.1494, found 222.1494. A sample of the **1** was dissolved in a small amount of MeOH, and an excess of TFA was added slowly under stirring. The mixture was then concentrated and dried in vacuo giving **1·TFA** as a yellowish oil: $[\alpha]^{20}_D$ 57.4 (*c* 0.72, MeOH) (lit.[2] $[\alpha]^{27}_D$ 71.2 (*c* 0.0399, MeOH). NMR spectra were in full accordance with those reported in the literature.[1a,2]

4*R*,5*S*-*epi*-Pinnamine (19). Deprotection of **18** (16.2 mg, 0.058 mmol) following the general procedure yielded the free amine **19** (10.1 mg, 79%) as a colorless oil: R_f (CH_2Cl_2/MeOH/Et_3N 20:1:0.1) = 0.10; ^{1}H NMR (300 MHz, MeOD) δ 7.36 (1H, s, C=C*H*), 4.82 (1H, ddd, J = 9.0, 5.7, 0.9 Hz), 3.90 (1H, ddd, J = 9.1, 1.7, 1.7 Hz), 3.70 (1H, m), 2.71 (1H, dd, J = 5.7, 1.7 Hz, C(=O)C*H*), 2.37−1.50 (10H, m), 1.02 (3H, t, J = 7.5 Hz, CCH_2CH_3); HRMS (FAB$^+$) calcd for $C_{13}H_{20}NO_2$ [M + H]$^+$ *m/z* 222.1494, found 222.1496. Due to the instability of this compound, further characterization was not possible.

2-Ethoxy-5-(*S*)-(5-oxohex-3-enyl)pyrrolidine-1-carboxylic Acid Methyl Ester (20). To a suspension of LiCl (56 mg, 1.32 mmol; dried overnight in vacuo at 140 °C) in MeCN (8.5 mL) under N_2 at rt were added dimethyl (2-oxopropyl)-phosphonate (0.18 mL, 1.30 mmol), ^{i}Pr$_2$NEt (0.19 mL, 143 mg, 1.11 mmol), and then a solution of **7** (252 mg, 1.10 mmol) in MeCN (4.5 mL). Stirring was then continued at rt under N_2 for 6 h. The reaction mixture was poured into brine (40 mL), and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated, and dried in vacuo. Flash chromatography of the residue yielded **20** (261 mg, 88%) as a colorless oil: R_f (heptane/EtOAc 3:2) = 0.26; $[\alpha]^{20}_D$ −35.7 (*c* 1.05, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (1H, ddd, J = 15.8, 6.5 Hz), 6.08 (1H, d, J = 15.8 Hz), 5.45−5.19 (1H, m), 3.92−3.74 (1H, m), 3.70 (3H, s), 3.65−3.35 (2H, m), 2.30−1.50 (8H, m), 2.23 (3H, s), 1.16 (3H, t, J = 7.0 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 198.6 (C), 156.5/155.7 (C), 147.9/147.7 (CH), 131.3 (CH), 88.3/87.7 (CH), 62.8/62.5 (CH_2), 57.7/57.2, (CH), 52.4 (C), 34.3/33.9 (CH_2), 32.2/31.8 (CH_2), 29.1/28.3 (CH_2), 28.5 (CH_2), 26.7 (CH_3), 15.1 (CH_3); IR (neat) 1698 (s), 1680 (s), 1628 (m). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.20; H, 8.34; N, 5.29.

2-Acetyl-9-azabicyclo[4.2.1]non-2-ene-9-carboxylic Acid Methyl Ester (21). MeOH (20 mL) was saturated with HCl (g) at −50 °C, and a drying tube was fitted to the flask. A solution of **20** (256 mg, 0.95 mmol) in MeOH (1.0 mL) was then added, and the reaction mixture was stirred overnight while heating slowly to rt (solution kept at −50 °C for the first hour). The mixture was then poured slowly into stirred cold satd $NaHCO_3$ (100 mL), and the mixture was neutralized by slow addition of further satd $NaHCO_3$ (300 mL). The mixture was then extracted with CH_2Cl_2 (3 × 400 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated, and dried in vacuo. Flash chromatography of the residue yielded a complex mixture (149 mg; R_f (heptane/EtOAc 1:1) = 0.46/0.34/0.27). This product mixture was dissolved in toluene (25 mL) under N_2 at rt, and DBU (0.20 mL, 1.34 mmol) was added. The mixture was then refluxed for 6.5 h. After being cooled to rt, the mixture was concentrated and dried in vacuo. Flash chromatography of the residue yielded **21** (108 mg, 51%) as a colorless solid: R_f (heptane/EtOAc 1:1) = 0.27; mp = 48−56 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89−6.77 (1H, m), 5.30−5.16 (1H, m), 4.53−4.30 (1H, m), 3.67/3.62 (3H, 2 × s), 2.52−1.98 (5H, m), 2.29 (3H, s), 1.76−1.61 (3H, m); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 197.8 (C), 154.1/154.0 (C), 148.9/148.6 (C), 142.6/141.7 (CH), 55.8/55.3 (CH), 54.1/53.1 (CH), 52.2 (CH_3), 31.9/31.7 (CH_2), 30.8/30.6 (CH_2), 29.6/28.5 (CH_2), 25.4 (CH_3), 24.1 (CH_2); IR (neat) 1702 (s), 1660 (s), 1629 (m); HRMS (FAB$^+$) calcd for $C_{12}H_{18}NO_3$ [M + H]$^+$ *m/z* 224.1287, found 224.1289.

Anatoxin-a (2). Deprotection of **21** (31.8 mg, 0.142 mmol) following the general procedure yielded the slightly impure free amine **2** (20.6 mg), which was dissolved in CH_2Cl_2 (2.0 mL), and the mixture was poured into satd $NaHCO_3$ (2.0 mL). The organic phase was isolated, and the aqueous phase was extracted with CH_2Cl_2 (5 × 2.0 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated, and dried in vacuo, yielding pure **2** (15.2 mg, 65%) as a yellowish oil: R_f (CH_2Cl_2/MeOH/Et_3N 20:1:0.2) = 0.21; ^{1}H and ^{13}C NMR spectra were in full accordance with those reported in the literature;[29] IR (neat) 1662 (s), 1636 (m); HRMS (FAB$^+$) calcd for $C_{10}H_{16}NO$ [M + H]$^+$ *m/z* 166.1232, found 166.1237.

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Supporting Information Available: General experimental methods; ^{1}H NMR spectra of **1**, **2**, **19**, and **21**; ^{13}C NMR spectra of **1**, **2**, and **21**; COSY spectra of **1** and **19**; and CIF data for **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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