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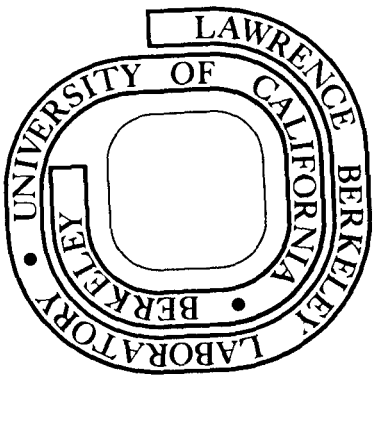

DISCLAIMER

THE SYNTHESIS OF ANATOXIN-a VIA INTRAMOLECULAR CYCLIZATION OF IMINIUM SALTS

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Abstract: Anatoxin-a (1) has been synthesized by exploiting intramolecular cyclization between an iminium salt and a nucleophilic carbon to construct the 9-azabicyclo[4.2.1]nonane ring system. Cyclization of malonate iminium salt 16 at alkaline pH afforded a low yield of bicyclic malonate 18 due to an unfavorable equilibrium constant and lability of the iminium salt in base. In contrast, cyclization of keto-iminium salt 31 afforded a good yield of bicyclic ketone 34 in acidic methanol. Dihydropyrrolium salts 16 and 31 were generated quantitatively by decarbonylation of substituted N-methylprolines 15 and 30b, obtained by reduction of the corresponding pyrroles.

Certain strains of Anabaena flos-aquae, a fresh water blue-green alga, produce a potent postsynaptic depolarizing neuromuscular toxin known as very fast death factor (VFDF) or anatoxin-a (1),[1] the structure of which was determined by X-ray crystallography and spectroscopy.[2,3] Fatal poisoning of various animals has been caused by ingestion of water from eutrophic ponds containing high concentrations of this alga.

[Structure 1]

In contrast to the many examples of the 8-azabicyclo[3.2.1]-octane ring system found in the diverse and widely distributed atropine alkaloids, anatoxin-a is the only naturally occurring representative of the homologous 9-azabicyclo[4.2.1]nonane series. Only two syntheses of this class of compounds have been reported, and both utilized ring expansion of the more readily available 8-azabicyclo[3.2.1]octanes. Thus 9-azabicyclo[4.2.1]nonan-3-one was first prepared by Tiffeneau ring expansion from tropinone.[4] More recently, a partial syntheses of anatoxin-a via ring expansion from cocaine was reported.[5]

We chose to examine a direct and potentially broader approach to anatoxin-a involving closure of the eight-membered carbon ring (seven-membered, counting through nitrogen) into an appropriately substituted pyrrolidine. Initially, we considered ring closure via a Dieckmann cyclization of the appropriate pyrrolidine-2,5-diester 4b as shown in Scheme I. However, this was unsuccessful, as might have been anticipated from the low yield of the analogous Dieckmann cyclization leading to tropinone-2-carboxylate[6,7] and the known difficulty of extending this reaction to medium-sized rings.

[Scheme I]

This communication describes the successful synthesis of

anatoxin-a via intramolecular cyclization between an iminium salt and a carbon atom bearing electron-withdrawing substituents as shown in the generalized Scheme II. Similar cyclizations have been successfully employed for the closure of relatively unstrained 5- and 6-membered rings, and occasionally bridged systems,[8,9] and the facility with which these cyclizations occur encouraged us to pursue this approach toward the more challenging strained and bridged 9-azabicyclo[4.2.1]nonane skeleton of anatoxin-a. The major encumbrance to synthetic utilization of iminium salts, the absence of a versatile method for their generation, was recently surmounted with the introduction of a high-yield, regiospecific method based on decarbonylation of α-amino acids,[10] and this approach was exploited in the present investigation as shown in Scheme II. The conditions and substituents necessary for effecting the key cyclization reaction were examined in detail.

[Scheme II]

Results and Discussion

Prior to examining intramolecular cyclization of iminium salts for the synthesis of anatoxin-a, we attempted to extend the scope of the Dieckmann cyclization, successfully utilized in the synthesis of tropinone-2-carboxylate,[6,7] to the preparation of homologous β-keto ester 5. Unsymmetrical t-butyl methyl diester 4b was selected as a precursor in order to direct the cyclization in the desired manner.[11] Thus (Scheme I) methyl 3-(2-pyrrolyl)-propanoate (2), obtained from pyrrole-2-carboxaldehyde by condensation with hydrogen methyl malonate followed by hydrogenation, was treated with t-butyl diazoacetate in the presence of a copper

catalyst to afford pyrrole diester 3. This normally low yield reaction was improved by adding an excess of t-butyl diazoacetate slowly to a solution of the pyrrole in benzene. Pyrrole diester 3 was hydrogenated over Pt in acetic acid to cis-pyrrolidine-2,5-diester 4a and subsequently N-methylated to give 4b. However, Dieckmann cyclization of 4b under a variety of conditions was unsuccessful, presumably due to excessive steric strain in the desired product, 5, as noted above.

The success of intramolecular cyclizations between iminium salts and nucleophilic carbons,[8,9] particularly in the classical synthesis of tropinone from succindialdehyde, 3-oxoglutaric acid, and methyl amine,[12] in which iminium salt intermediate 6 has been proposed, suggested an iminium salt approach to anatoxin-a as shown in Scheme II. Initially, we examined the intramolecular cyclization of malonate iminium salt 16 prepared by decarbonylation of substituted N-methylproline 15. The N-methyl substituent was selected to provide the tertiary amino acid substrate required for decarbonylation. N-Methylproline 15 was prepared by reducing pyrrole acid 14 which was synthesized as shown in Scheme III.

1-Methylpyrrole-2-carboxaldehyde (7) was condensed with hydrogen methyl malonate to afford acrylate 8 (a Wittig reaction was more cumbersome and gave a lower yield) which was catalytically reduced to propanoate 9 over Pd/C, and further reduced to alcohol 10 with $LiAlH_4$. Converting alcohol 10 into a leaving group capable of displacement by dimethyl malonate anion proved to be unexpectedly difficult. Formation of the bromide or chloride with numerous reagents gave low yields of product, due to sensitivity of the electron-rich

pyrrole to oxidation and acid-catalyzed polymerization. Even the best conditions, PBr_3/pyridine or CBr_4/triphenylphosphine, gave ~20% yield. The methanesulfonate 11a was easily prepared as was the toluenesulfonate derivative, but these gave only low yields of 12 when treated with dimethyl malonate anion. Therefore the methanesulfonate 11a was converted to iodide 11b which gave an excellent yield of malonate 12 upon displacement with sodio dimethyl malonate.

Pyrrole 12 was treated with trichloroacetyl chloride[13] to afford the 5-trichloroacetylpyrrole 13. The trichloroacetyl group was then hydrolyzed to pyrrole acid 14 with a slight excess of NaOH in a mixture of water and acetone. Kinetic studies demonstrated that no appreciable hydrolysis of the malonate methyl ester would occur, since hydrolysis of the trichloroacetyl function is one hundred times faster. Hydrogenation of pyrrole 14 to pyrrolidine 15 was best accomplished in methanol with rhodium/alumina catalyst. Platinum was not an effective catalyst in methanol, and in acetic acid substantial decarboxylation of 14 accompanied hydrogenation. Decarbonylation of amino acid 15 with $POCl_3$ at 105°[10] afforded a quantitative yield of iminium salt 16, which was not isolated, but was completely characterized spectroscopically and by catalytic reduction to pyrrolidine 17.

Because iminium salt 16 decomposes rapidly under the alkaline conditions necessary for isolating bicyclic malonate 18, hydrogenation of 16 was also utilized in order to monitor its cyclization to 18. Since the bicyclic malonate 18 is unaffected by this brief hydrogenation, the yield of 18 and amount of iminium salt 16 remaining could be simultaneously determined. Table I

shows the yield of bicyclic malonate 18 and the amount of iminium salt remaining after 5 minutes of reaction between pH 3.0 and 8.8 at 20°. The results demonstrate that little cyclization occurs below pH 7.5, but that above this pH, the iminium salt decomposes very rapidly, forming only small amounts of product. Thus, the maximum conceivable yield of 18 would be 14% at pH 8.0, based on the amount of iminium salt remaining unreacted. The polymerization of similar iminium salts in alkaline media is a well-known phenomenon.[14,15]

Longer reaction times and higher temperatures did not increase the yield of 18, but unexpectedly, had just the opposite effect. This observation suggested that the cyclization was reversible. Indeed, when the isolated bicyclic malonate 18 was placed in water at pH 7 or 10, it decomposed with a half-life of 10 and 5 minutes, respectively. Furthermore, in aqueous acid (pH 1-3) 18 formed iminium salt 16 in nearly quantitative yield with a half-life of 2 hours. In summary, as shown in Scheme IV, the low yield of 18 is due to an equilibrium very unfavorable toward its formation as well as irreversible polymerization which decimates the product at alkaline pH. By rapidly extracting 18 into dichloromethane or chloroform immediately after adding base to 16, it was possible to trap more of the product, and yields of 20 to 25% were obtained.

The obstacle to cyclization is clearly thermodynamic rather than kinetic, since equilibrium is rapidly attained and longer reaction does not increase the yield of 18. The facile ring closure of iminium salts leading to less strained products, for example 19 to 20, which occurs in 77% yield at pH 6.5 after 12 h[10] also supports this conclusion. Thus we considered three types of

structural modification designed to overcome this unfavorable equilibrium: (1) increasing the reactivity of the iminium salt by changing the substituent attached to nitrogen, (2) increasing the acidity of the nucleophilic carbon to allow cyclization at a lower pH, and (3) decreasing steric strain in the product. Considering the third alternative, we reasoned that steric strain could be reduced if the two ester groups of 16 were replaced by a single electron-withdrawing group. Several reports of intramolecular cyclization between iminium salts and ketones, ketals or enol ethers[8,9,16] suggested that bicyclic ketone 34 could be obtained via cyclization of keto iminium salt 31.

fn 16

In order to ascertain whether the bicyclic ketone 34 actually exhibited the predicted increased stability over bicyclic malonate 18, a sample of 34 was prepared from 18. Thus the bicyclic malonate 18 was hydrolyzed and decarboxylated in 6M HCl, then re-esterified to afford bicyclic ester 21a. The ester 21a was hydrolyzed to lithium salt 21b with LiOH and subsequently treated with methyl lithium, leading to the desired bicyclic ketone 34. In accord with prediction, 34 was found to be two orders of magnitude more stable than 18. The half-life of 34 is 5 h at pH 10 (compared to 5 min for 18) and no decomposition could be observed in acid at 20°. Thus we proceeded to prepare keto iminium salt 31, confident that it would cyclize to bicyclic ketone 34.

[Structures 21a,b]

Although keto iminium salt 31 might have been prepared *via* nucleophilic displacement from iodide 11b, we employed a more direct approach for elaborating the ketone side chain, as shown in Scheme V. Friedel-Crafts acylation of 1-methylpyrrole with the acid

[Scheme V]

chloride of hydrogen methyl glutarate (22) afforded an 80:20 mix of positional isomers 23 and 24, easily separated by distillation. Evidently, the steric bulk of the entering glutarate moiety is responsible for the unusual abundance of the normally rare 3-isomer 24.[17] Similar mixtures were obtained from the corresponding Friedel-Crafts acylation with glutaric anhydride or Vilsmeier acylation with methyl N,N-diethylglutaramate.

Wolff-Kishner reduction of ketone 23 afforded 5-(1-methyl-2-pyrrolyl)pentanoic acid (25) in quantitative yield. The lithium salt of 25 was treated with a slight excess of methyllithium, producing ketone 26, and acylation with trichloroacetyl chloride afforded 27 which reacted with methoxide to give methyl ester 28. Catalytic reduction of this pyrrole to pyrrolidine 29 was accomplished using rhodium-alumina in acidic methanol. The ketone functionality was restored by oxidizing alcohol 29 with Jones reagent to ketone 30a. Protecting the ketone in 28 as its dimethyl ketal prior to hydrogenation was less satisfactory. The keto methyl ester 30a was then hydrolyzed with aqueous HCl, providing the hydrochloride of keto amino acid 30b which was decarbonylated with $POCl_3$ to afford iminium salt 31. Catalytic reduction to pyrrolidines 32 and 33 demonstrated that the yield of 31 was quantitative.

As had been predicted, initial results of the cyclization were encouraging: iminium salt 31 afforded a 15% yield of bicyclic ketone 34 after 14 hours at 20° in water at pH 0.5. After some experimentation, a respectable 47% yield was attained by refluxing 31 in acidic methanol for 14 hours. In contrast, the same conditions afforded bicyclic malonate 18 in 2% yield.

Catalytic reduction of the reaction mixture demonstrated that after 14 and 42 h of reflux, 43% and 15%, respectively, of the original iminium salt remained unreacted. These results indicate that, again, a reversible equilibrium and a non-reversible polymerization of the iminium salt occur in analogy to Scheme IV. However, the equilibrium constant for 31 → 34 is approximately 3 and the polymerization is slow, whereas the equilibrium constant for 16 → 18 is less than 0.2 and polymerization is rapid at the alkaline pH requisite for cyclization.

The successful synthesis of bicyclic ketone 34 formally competes the synthesis of anatoxin-a (1), since 34, prepared by ring expansion from cocaine, has been converted to anatoxin-a.[5] Contrary to the previous observations, however, 34 prepared from 31 or 18 was totally homogeneous, NMR revealed only one epimer, and no epimerization occurred, suggesting that perhaps the 34 obtained previously may have been impure.

Bicyclic ketone 34 was treated with 2,2,2-trichloroethoxycarbonyl chloride, and the resulting carbamate 35a was hydrolyzed with Zn in acetic acid to give dihydroanatoxin-a (35b). This compound was found to possess an LD_{50} of approximately 2.5 mg/kg (ip, mouse, HCl salt) compared to 0.2 mg/kg for anatoxin-a (1).

[Structures 35a,b]

In conclusion, intramolecular cyclization of an iminium salt has been successfully utilized as the key step in the synthesis of anatoxin-a, and the reaction conditions and structural parameters favoring this cyclization were determined. The success of the present method suggests the general utility of this approach for the synthesis of variously bridged alkaloids.

Experimental Section

General Procedures. Gas chromatography was performed using a Hewlett-Packard 402 gas chromatograph equipped with a 6' 5% SE-30 column at 40 psi He. Pre-coated EM Reagent silica gel 60 F-254 TLC plates were used. The pyrroles were visualized by short wave UV light and by spraying with a reagent prepared from $Ce(SO_4)_2 \cdot 2\ H_2O$ (2.1 g), concentrated sulfuric acid (2.8 ml) and water (100 ml) followed by heating. Other compounds were visualized by spraying with a 10% solution of phosphomolybdic acid in 95% ethanol followed by heating. NMR spectra were recorded with a Varian T-60 spectrometer in $CDCl_3$ (TMS as internal standard) or in D_2O (sodium 3-(trimethylsilyl)propanesulfonate (DDS) as internal standard) unless otherwise specified. IR spectra were recorded as thin films. Reaction temperatures were bath temperatures unless internal is specified.(i.t.). Reactions were carried out under a nitrogen atmosphere, using magnetic stirring. Organic solutions were dried over anhydrous magnesium sulfate, and solvents were evaporated *in vacuo* using a Berkeley rotary evaporator. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

Hydrogen Methyl Malonate was prepared by a modification of the procedure used to prepare hydrogen ethyl malonate.[18] Methanolic KOH (179 g, 3.2 mol, in 2.1L) was added to methanolic dimethyl malonate (423 g, 3.2 mol, in 2.1L) over 1 h. After 18 h, the potassium salt (375 g, 2.4 mol) was pptd. by cooling (-13°) and concentrating the mixture, then washed with ether. The aqueous potassium salt (375 g in 375 mL) was slowly (1 h) acidified (pH 1.5)

with conc HCl (2.4 mmol) at i.t. 5-10° and the product was extracted from the aqueous solution and the KCl ppt with ether to give 232 g, 62% yield.

Methyl 3-(2-Pyrrolyl)propanoate (2). Pyrrole-2-carboxaldehyde (81.2 g, 0.855 mol) was condensed with hydrogen methyl malonate (201 g, 1.71 mol, 200 mol %) in pyridine (425 mL) and piperidine (10 mL) at i.t. 50-60° for 42 h and 70-80° for 28 h. Ether (1.8L) was added and the pyridine and piperidine extracted into 1.8 M HCl (2x2 L). The organic phase was washed with aq. Na_2CO_3, dried, and the ether was evaporated, leaving crude dark purple methyl (E)-β-(2-pyrroyl)-acrylate (97 g) contaminated with dimethyl 3-(2-pyrrolyl)glutarate. The crude product was dissolved in methanol (1 L) and hydrogenated (50 psi, 6 h) over 10% Pd/C (9 g). Removal of catalyst and evaporation of solvent followed by distillation (75°/0.3 mm) afforded the product 2 as a clear liquid (58.5 g, 45% yield): mp 8-11° (lit.[19] bp 75°/0.3 mm); NMR δ 2.70 (4H, m), 3.64 (3H, s), 5.74 (1H, m), 5.89 (1H, m), 6.46 (1H, m).

Methyl 3-(5-t-Butoxycarbonylmethyl-2-pyrrolyl)propanoate (3). t-Butyl diazoacetate[20] (25.9 g, 182 mmol, 128 mol %) was added over 3 h to a mixture of methyl 3-(2-pyrrolyl)propanoate (2) (21.7 g, 142 mmol) and copper powder (1.35 g) in benzene (45 ml) at i.t. 70°. After 1 h more, the solvent was evaporated, starting material (5.2 g) removed (72°/0.2 mm) and the product kugelrohr distilled (110°, 0.2 mm) to give a yield of 23.1 g, 61% based on 2 added, 80% based on 2 consumed: NMR (CCl_4) δ 1.45 (9H, s), 2.71 (4H, m), 3.46 (2H, s), 3.68 (3H, s), 5.72 (2H, m), 8.9 (1H, br). Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.9; H, 7.9; N, 5.2. Found: C, 63.1; H, 7.8; N, 5.3.

Methyl 3-(5-t-Butoxycarbonylmethyl-2-pyrrolidinyl)propanoate (4a). The pyrrole 3 was hydrogenated (35 psi, 5h) over Pt in acetic acid. After isolation by partition between aqueous acid/CH_2Cl_2 and aq. alkali/CH_2Cl_2, the product was kugelrohr distilled (90-100°/0.1 mm) in 78% yield: NMR (CCl_4) δ 1.44 (9h, s), 1.0-2.5 (10H, m), 3.2 (2H, m), 3.68 (3H, s); MS m/e 271 (0.4, M^+), 214 (17); Anal. Calcd. for $C_{14}H_{25}NO_4$: C, 62.0; H, 9.3; N, 5.2. Found: C, 61.9; H, 9.0; N, 5.1.

Methyl 3-(5-t-Butoxycarbonylmethyl-1-methyl-2-pyrrolidinyl)-propanoate (4b). Pyrrolidine 4a (3.51 g, 13.0 mmol) was dissolved in CH_3OH (40 mL) and aqueous formaldehyde (62 mmol, 450 mol %) was added. The mixture was hydrogenated (30 psi, 19 hr) over 10% Pd/C (500 mg), the catalyst was removed and the solvent evaporated. The product (3.12 g, 84%) was kugelrohr distilled (110°/0.1 mm): NMR (CCl_4) δ 1.41 (9H, s), 1.3-2.8 (12H, m), 2.21 (3H, s), 3.58 (3H, s); MS m/e 285 (1.8, M^+), 198 (50), 142 (100); Anal. Calcd. for $C_{15}H_{27}NO_4$: C, 63.2; H, 8.5; N, 4.9. Found: C, 63.6; H, 9.5; N, 5.0.

Attempted Dieckmann Cyclization of 4b. The starting material, t-butyl methyl ester 4b, was added to a mixture of toluene, t-butanol (10 mol %) and KH (110 mol %) and refluxed beneath 4A molecular sieves over 28 h. After an additional 24 h of reflux, the reaction was quenched, affording only starting material (55%) and none of the desired β-keto ester 5 (MS, $FeCl_3$). Under the same conditions, methyl t-butyl suberate cyclized to the t-butyl β-ketoester in 55% yield.

Methyl (E)-β-(1-Methyl-2-pyrrolyl)acrylate (8). A mixture of fn 21 1-methylpyrrole-2-carboxaldehyde[21] (7, 101 g, 927 mmol), hydrogen methyl malonate (125 g, 1 mol, 114 mol %), pyridine (400 mL) and piperidine (18.5 mL, 187 mmol, 20 mol %) were stirred under N_2 at i.t. 70° for 35 h. Evolution of CO_2 was essentially complete after 25 h. Solvent was evaporated, followed by drying at 50°/5 mm/2 h. Distillation afforded some recovered aldehyde (80°/2 mm) followed by the acrylate 8 (120°/2 mm): 101 g, 77% yield based on starting material consumed; GC (180°) 2.5 min; NMR δ 3.66 (3H, s, NCH_3), 3.71 (3H, s, CO_2CH_3), 6.03 (1H, d, J=16, C=CH), 6.1 (1H, m), 6.6 (1H, m), 7.50 (1H, d, J=16 C=CH); MS m/e 165 (76, M^+), 134 (100, M^+-CH_3O). Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.4; H, 6.7; N, 8.5. Found: C, 65.2; H, 6.7; N, 8.4.

Methyl 3-(1-Methyl-2-pyrrolyl)propanoate (9) was prepared by hydrogenating methyl (E)-β-(1-methyl-2-pyrrolyl)acrylate (8, 10 g) in methanol over 10% Pd/C (1 g in 100 mL) for 2 h at 50 psi. Removal of the catalyst and evaporation of the CH_3OH left the product: 9.5 g, 94%; bp 75-80°/2.5 mm by kugelrohr distillation; GC (180°) 1.0 min; NMR δ 2.74 (4H, m, CH_2CH_2), 3.53 (3H, s, NCH_3), 3.69 (3H, s, CO_2CH_3), 5.9 (1H, m), 6.05 (1H, t), 6.55 (1H, t); MS m/e 167 (18, M^+), 94(100). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.7; H, 7.8; N, 8.4. Found: C, 64.5; H, 7.9; N, 8.3.

3-(1-Methyl-2-pyrrolyl)propanol (10). Crude methyl propanoate (9, 8.9 g, 53.2 mmol) was dissolved in 75 mL dry ether and filtered and the filtrate was added to a suspension of $LiAlH_4$ (2.5 g, 64 mmol, 120 mol %) in 75 mL ether over 1/2 h. After stirring 2 hr more at 20°, to the reaction mixture was added 9 mL

H_2O and 4 mL 10% NaOH, removing the precipitate, then evaporating the solvent to afford the propanol 10: 6.7 g, 89% yield; GC (150°) 0.9 min, (200°) 0.25 min; bp 80-120°/1.1 mm by kugelrohr distillation; NMR δ 1.8 (1H, br, OH), 1.85 (2H, m), 2.65 (2H, br t, J=7), 3.54 (3H, s, NCH_3), 3.70 (2H, t, J=6), 5.9 (1H, m), 6.02 (1H, t), 6.52 (1H, t); MS m/e 139 (14, M^+), 94(100). Anal. Calcd for $C_8H_{13}NO$: C, 69.0; H, 9.4; N, 10.1. Found: C, 68.9; H, 9.3; N, 10.1.

3-(1-Methyl-2-pyrrolyl)propanol Methanesulfonate (11a). Crude propanol 10 (51 g, 367 mmol) was dissolved in 500 mL CH_2Cl_2 and triethylamine (80 mL, 570 mmol, 155 mol %) was added. After cooling to 0°, methanesulfonyl chloride (37 mL, 48 mmol, 130 mol %, distilled) was added over 20 min. After 1 h additional stirring at 0°, the mixture was washed with satd. NaCl, satd Na_2CO_3, satd. NaCl (100 mL each), and dried. The solvent was removed to afford the product as an orange oil (81 g, 102% crude yield): bp 159°/1.0 mm by kugelrohr distillation; NMR δ 2.1 (2H, m), 2.7 (2H, br t), 2.97 (3H, s, OSO_2CH_3), 3.53 (3H, s, NCH_3), 4.29 (2H, t, J=7), 5.85 (1H, m), 6.02 (1H, t), 6.52 (1H, t); MS m/e 217 (7, M^+), 94 (100). Anal. Calcd for $C_9H_{15}NO_3S$: C, 49.8; H, 7.0; N, 6.5. Found: C, 49.5; H, 7.0; N, 6.5.

2-(3-Iodopropyl)-1-methylpyrrole (11b). The crude methanesulfonate (11a, 81 g, 373 mmol) was dissolved in 550 mL absolute ethanol and sodium iodide (112 g, 750 mmol, 200 mol %) was added. A mildly exothermic reaction ensued. After stirring 20 h at 40°, the ethanol was evaporated, the residue was partitioned between ether and water, and the organic phase evaporated then kugelrohr distilled

to afford the iodide as a nearly colorless liquid: 51.5 g, 56% yield; GC (200°) 0.55 min; NMR δ 2.15 (2H, m), 2.65 (2H, br t), 3.22 (2H, t, J=7), 3.52 (3H, s, NCH_3), 5.85 (1H, m), 5.97 (1H, t), 6.47 (1H, t); MS m/e 249 (16, M^+), 94(100). Anal. Calcd. for $C_8H_{12}NI$: C, 38.6; H, 4.9; N, 5.6. Found: C, 38.4; H, 4.9; N, 5.6.

Methyl 2-Methoxycarbonyl-5-(1-methyl-2-pyrrolyl)pentanoate (12). Sodium (9.5 g, 413 mmol, 187 mol %) was dissolved in 250 mL methanol at 0°. Dimethyl malonate (50.5 mL, 442 mmol, 200 mol %) was added and the solution stirred at room temperature 30 min. The propyl iodide (11b, 55 g, 221 mmol) in 150 mL methanol was added and the solution refluxed 1/2 h, then cooled to 0°, a 1.0M methanolic H_2SO_4 solution was added to pH 8, the methanol was evaporated and replaced with ether, and after extraction with water, the excess dimethyl malonate was distilled (50°/0.2 mm) leaving the pyrrole malonate 12 (53.7 g, 96% yield), purified by kugelrohr distillation: GC (200°) 2 min; TLC (Et_2O) 0.65 (Et_2O/pet ether 1/1) 0.45; NMR δ 1.5-2.2 (4H, m), 2.55 (2H, br t), 3.40 (1H, m), 3.50 (3H, s, NCH_3), 3.73 (6H, s, CO_2CH_3), 5.85 (1H, m), 5.99 (1H, t), 6.50 (1H, t); MS m/e 253 (9, M^+), 94 (100). Anal. Calcd. for $C_{13}H_{19}NO_4$: C, 61.6; H, 7.6; N, 5.5. Found: C, 61.5; H, 7.6; N, 5.5.

Methyl 2-Methoxycarbonyl-5-(1-methyl-5-trichloroacetyl-2-pyrrolyl)pentanoate (13). A modification of the previous method[13] was used. Potassium carbonate (ground finely then dried at 350°, 12 h, 58.5 g, 424 mmol, 200 mol %) was suspended in 500 mL ether and trichloroacetyl chloride (29 mL, 260 mmol, 125 mol %) added, followed by the pyrrole malonate (12, 53.7 g, 212 mmol) in 100 mL

ether over 10 min. The mixture was stirred 2 h then filtered, extracted with satd. sodium bicarbonate and dried to afford the trichloroacetyl derivative 13: 82.5 g, 97.5% yield; mp 77-78° from pet ether; UV (CH_3OH) 322 nm (ε 15,000); TLC (Et_2O/pet ether 1/1) 0.38; NMR δ 1.5-2.2 (4H, m), 2.62 (2H, br t), 3.37 (1H, t), 3.71 (6H, s, CO_2CH_3), 3.81 (3H, s, NCH_3), 5.99 (1H, d, J=4,5), 7.31 (1H, d, J=4,5); MS m/e 397 (3, M^+), 399 (3, M^+), 401 (1, M^+), 280 (100, M^+-CCl_3).

Methyl 2-Methoxycarbonyl-5-(5-carboxy-1-methyl-2-pyrrolyl)-pentanoate (14). The trichloroacetyl pyrrole (13, 80 g, 200 mmol) was dissolved in 500 mL acetone and 100 mL water was added, followed by 1.00M NaOH (220 mL, 220 mmol, 110 mol %) over 20 min. The reaction may be followed by observing disappearance of 13 at 322 nm. After addition, UV indicated 96% consumption of 13. After 10 more min, the acetone and some of the water was evaporated, and the aqueous solution extracted with ether. The product precipitated when 1M HCl was slowly added to pH 3. After collection by filtration and drying, product (52 g, 88% yield) was obtained of mp 124-127°. Recrystallization from ethyl acetate gave pure pyrrole acid 14: mp 142-144°; TLC (Et_2O) 0.5; UV (CH_3OH), λ_{max} 226 nm (ε 13,000); NMR δ 1.5-2.2 (4H, m), 2.60 (2H, br t), 3.37 (1H, t), 3.72 (6H, s, CO_2CH_3), 3.78 (3H, s, NCH_3), 5.89 (1H, d, J=4,5), 6.98 (1H, d, J=4.5), 8.2 (1H, br, CO_2H); MS m/e 297 (7, M^+), 280 (25, M^+-OH), 94 (100). Anal. Calcd. for $C_{14}H_{19}NO_6$: C, 56.6; H, 6.4; N, 4.7. Found: C, 56.5; H, 6.4; N, 4.6.

Methyl 2-Methoxycarbonyl-5-(5-carboxy-1-methyl-2-pyrrolidinyl)-pentanoate (15). The pyrrole acid (14, 8.9 g, 30 mmol) was

suspended in 450 mL methanol and hydrogenated (50 psi) over 5% Rh/Al_2O_3 (8.9 g) for 4 days. The reduction was monitored by UV which indicated that about 15% of the starting material remained unreduced. The catalyst was removed by filtration and the solvent evaporated, leaving a white semisolid which was suspended in water (250 ml), to remove the remaining insoluble starting material (1.6 g, 18%). After washing with CH_2Cl_2, the water was evaporated, leaving a hygroscopic glass, the hydrate of proline derivative 15 (6.5 g, 68% crude). This was dissolved in 60 mL CH_2Cl_2 in which was passed HCl (g) for 1 min then cooled to 0° for 2 h. Ether was added to flocculate the precipitate which was filtered, washed with acetone then CH_2Cl_2 and dried to afford 15 HCl (6.5 g, 64% yield, 78% based on 14 consumed): mp 166-170°d; TLC ($CHCl_3/CH_3OH/NH_4OH$, 80/19/1) 0.35; NMR δ 1.2-2.5 (10H, m), 2.91 (3H, s, NCH_3), 3.0-4.4 (3H, m), 3.73 (6H, s, CO_2CH_3); IR 3400, 2940, 1720, 1620 cm^{-1}. Anal. Calcd. for $C_{14}H_{24}NO_6Cl$: C, 49.8; H, 7.2; N, 4.1. Found: C, 49.7; H, 7.2; N, 4.0.

5-[4-Bis(methoxycarbonyl)butyl]-3,4-dihydro-1-methyl-2H-pyrrolium (16) was prepared from amino acid hydrochloride 15 following the procedure used to prepare 31 below. The light brown crude iminium salt 16 showed IR ($POCl_3$) 1750 (s), 1730 (s), 1680 (w) cm^{-1}; NMR ($POCl_3$) δ 1.2-3.5 (12H, m), 3.52 (3H, br s, NCH_3), 3.62 (6H, s, CO_2CH_3), 8.48 (1H, br s, N=CH).

Methyl 2-Methoxycarbonyl-5-(1-methyl-2-pyrrolidinyl)pentanoate (17). A. The crude iminium salt 16 (from 100 mg 15, 0.30 mmol) was cooled to 0° and dissolved in water (2 mL, pH 1.0) then hydrogenated (40 psi) over 20 mg PtO_2 for 1 hr. After removal of the catalyst

and basification to pH 9.8, the product 17 was extracted into CH_2Cl_2: 74 mg, 97% yield.

B. The crude aqueous iminium salt was basified (pH 6 to 9) and reacidified (pH 1.0) after 5 min, then hydrogenated as above for 10 min. The results are shown in Table I. Bicyclic malonate 18 does not form 17 on hydrogenation under these conditions.

C. Pyrrole 12 (270 mg) was hydrogenated in acetic acid (3 mL) with PtO_2 (30 mg) and H_2 (50 psi) for 24 h. The acetic acid was removed, and the residue subject to an acid-base partition followed by kugelrohr distillation (120°/0.1 mm) to afford the product as a clear oil (195 mg, 71% yield). TLC ($CHCl_3/CH_3OH/NH_4OH$, 80/19/1) 0.5; GC (200°) 1.6 min; NMR δ 1.1-2.1 (12H, m), 2.26 (3H, s, NCH_3), 3.0 (1H, m), 3.34 (1H, t), 3.70 (6H, s, CO_2CH_3).

Dimethyl 9-Methyl-9-azabicyclo[4.2.1]nonane-2,2-dicarboxylate (18). The crude iminium salt 16 (from 100 mg of 15, 0.30 mmol) was cooled to 0° and 0.5 mL water was added with stirring. Saturated Na_2CO_3 was rapidly added to pH 9.8 at 20°, and the mixture was immediately extracted three times with CH_2Cl_2. The organic phase was dried and the solvent evaporated, leaving crude product (23 mg) which was kugelrohr distilled (100-120°/0.1 mm) to afford bicyclo malonate 18 as a clear oil (18 mg, 24%): TLC ($CHCl_3/CH_3OH/NH_4OH$, 80/19/1) 0.75; GC (200°) 1.45 min. NMR δ 1.2-2.5 (10H, m), 2.49 (3H, s, NCH_3), 3.1 (1H, m), 3.65 (3H, s, CO_2CH_3), 3.68 (3H, s, CO_2CH_3), 3.8 (1H, m); MS m/e 255 (10, M^+), 224 (10, M^+-OCH_3), 96(50), 82(100). Anal. Calcd. for $C_{13}H_{21}NO_4$: C, 61.2; H, 8.3; N, 5.5. Found: C, 61.4; H, 8.3; N, 5.3.

Methyl 9-Methyl-9-azabicyclo[4.2.1]nonane-2-carboxylate (21a).

The bicyclic malonate (18, 98 mg) was dissolved in 6M HCl (2 ml) and rapidly heated to reflux under nitrogen. The HCl was evaporated after 7.5 h, affording the acid as a clear glass. This was esterified by refluxing in CH_3OH with catalytic sulfuric acid for 17h beneath a soxhlet extractor filled with 3A molecular seives. Evaporation of most of the solvent, basification with Na_2CO_3, and extraction into CH_2Cl_2 followed by kugelrohr distillation (70-90°/1.4 mm) afforded the bicyclo monoester 21a: 40.1 mg, 53%; GC (200°) 0.65 min. NMR δ 1.2-2.5 (11H, m), 2.40 (3H, s, NCH_3), 3.1-3.5 (2H, m), 3.65 (3H, s, CO_2CH_3); MS m/e 197 (18, M^+), 82 (100); Anal. Calcd for $C_{11}H_{19}NO_2$: C, 67.0; H, 9.7; N, 7.1. Found: C, 66.6; H, 9.6; N, 7.0.

4-Methoxycarbonylbutanoyl Chloride (22) was prepared by a modification of the previous procedure.[22] Glutaric anhydride (62.8 g, 550 mmol) and anhydrous methanol (17.6 g, 550 mmol) were heated at 100° for 1.5 hr. The monomethyl ester was cooled and $SOCl_2$ (50 ml, 685 mmol, 125 mol %) was added, resulting in an endothermic reaction and gas evolution. The temperature was slowly raised to 70° for 1 hr. After cooling, excess $SOCl_2$ was evaporated and the acid chloride distilled at 100°/14 mm: 71 g, 79% yield; NMR δ 1.8-2.6 (4H, m), 2.99 (2H, t), 3.67 (3H, s).

Methyl 4-(1-Methyl-2-pyrrolylcarbonyl)pentanoate (23). The acid chloride of hydrogen methyl glutarate (22) (26.2 g, 154 mmol) was dissolved in 100 ml CH_2Cl_2 and mixed with aluminum chloride (22 g, 165 mmol, 107 mol %). This mixture was added to a stirred solution of 1-methylpyrrole (15 g, 185 mmol, 120 mol %) in 100 ml CH_2Cl_2 at -40°, maintaining about i.t. -20°. After 15 min, 1.5 g

more 1-methylpyrrole was added and stirring continued 45 min at i.t. -25° and 1 hr at +20°. The solvent was removed, and 200 ml ice and water added to the cooled mixture, which was extracted into ether (4 x) and the ether layer washed with saturated sodium carbonate solution, saturated NaCl, and dried. The crude product (27.2 g) was a mixture of 2- and 3-isomers, 23 and 24: TLC (Et_2O) 23, 0.6; 24, 0.4; GC (210°) 23, 1.1; 24, 2.2 min. The 2-isomer, 23, was distilled through a vacuum-jacketed column fitted with a platinum screen (bp 120°, 0.4 mm): mp 37-39°; yield 16.5 g, 51%; NMR δ 2.2 (4H, m), 2.79 (2H, t), 3.61 (3H, s, CO_2CH_3), 3.88 (3H, s, NCH_3), 6.01 (1H, dd), 6.68 (1H, m), 6.86 (1H, dd). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.1; H, 7.2; N, 6.7. Found: C, 63.2; H, 7.2; N, 6.7.

Methyl 4-(1-Methyl-3-pyrrolylcarbonyl)pentanoate (24) was the major component of the higher boiling fraction, 7.1 g (22%), bp 165°/0.1 mm. A sample was purified by chromatography on silica gel, eluting with ether: NMR δ 2.2 (4H, m), 2.72 (2H, t), 3.61 (6H, s, $NCH_3CO_2CH_3$), 6.48 (2H, d, J=2Hz), 7.17 (1H, m).

5-(1-Methyl-2-pyrrolyl)pentanoic Acid (25). As in a similar case,[23] the ketone (23, 20.7 g, 99 mmol) was stirred with dry ethylene glycol (180 ml) and hydrazine hydrate (85% in water, 17 ml, 14.5 g, 290 mmol, 290 mol %) at 100° for 15 min. Potassium hydroxide (24 g, 430 mmol, 430 mol %) was added slowly and the bath temperature raised slowly (1.5 hr) to 210°, removing the water and excess hydrazine by distillation. Heating at i.t. 190° was continued 4.5 hr, the solution was cooled, acidified to pH 2.0, extracted with ether (5 x), dried, and the ether evaporated to afford essentially

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pure acid 25 as a light yellow solid, mp 58-61°, 17.9 g (100% yield). Kugelrohr distillation (110°/0.2 mm) afforded white crystals, mp 71-73°: NMR δ 1.7 (4H, m), 2.4 (4H, m), 3.46 (3H, s, NCH_3), 5.80 (1H, t), 6.41 (1H, t). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.3; H, 8.3; N, 7.7. Found: C, 66.2; H, 8.2; N, 7.7.

6-(1-Methyl-2-pyrrolyl)-2-hexanone (26). The carboxylic acid (25, 17.9 g, 99 mmol) was converted to its lithium salt with lithium hydroxide monohydrate (4.22 g, 101 mmol, 102 mol %) in 40 mL hot water; 10 min after homogeneity was achieved, the water was evaporated and the product further dried in a vacuum dessicator for 24 hr, yielding the lithium salt of 25 (17.9 g, 97% yield).

The lithium salt and triphenylmethane (18 mg) were suspended in 180 mL THF and methyl lithium (49 ml of 2.1M, 103 mmol, 104 mol %) was added over 0.5 hr until all the starting material dissolved and a persistent orange-red color appeared. After stirring 9 hr, the reaction mix was cooled to 0° and added to a stirred mixture of HCl (15 ml of 12M, 180 mmol, 180 mol %), water and ice (200 ml). The layers were separated, and the aqueous layer, after basification, was extracted 3 x with ether. The combined organic layers were dried, the solvent evaporated, and the crude product (15.7 g, 87%) was kugelrohr distilled (105°/1.5 mm) to afford ketone 26: 13.3 g, 75% yield; TLC (Et_2O) 0.65; GC (210°) 0.65 min; NMR δ 1.65 (4H, s), 2.11 (3H, s, $COCH_3$), 2.5 (4H, m), 3.50 (3H, s, NCH_3), 5.86 (1H, m), 6.01 (1H, t), 6.51 (1H, t). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.7; H, 9.6; N, 7.8. Found: C, 74.0; H, 9.6; N, 7.7.

6-(1-Methyl-5-trichloroacetyl-2-pyrrolyl)-2-hexanone (27). The pyrrole ketone (26, 8.7 g, 48.6 mmol) was dissolved in anhydrous

ether (87 ml) and trichloroacetyl chloride (6.0 ml, 54 mmol, 110 mol %) was added. After 1 hr the solvent was removed to afford 27 as a red oil, 16.5 g, 105% yield. Including 200 mol % anhydrous K_2CO_3 in the reaction resulted in a lower (71%) yield of slightly purer material: TLC (Et_2O) 0.60; NMR δ1.7 (4H, m), 2.16 (3H, s, $COCH_3$), 2.55 (4H, m), 3.87 (3H, s, NCH_3), 6.05 (1H, d), 7.47 (1H, d).

6-(5-Methoxycarbonyl-1-methyl-2-pyrrolyl)-2-hexanone (28). The crude trichloroacetyl pyrrole 27 was dissolved in 30 ml methanol and a solution of sodium methoxide prepared from sodium (450 mg, 19.5 mmol, 40 mol %) and 50 mL methanol was added over 5 min. The red color faded to amber and λ_{max} shifted from 322 to 272 nm. After stirring 0.5 hr, the methanol was evaporated and ether (100 ml) and water (50 ml) were added. The organic layer was washed with saturated NaCl, dried and the ether evaporated to afford 10.4 g crude product. Kugelrohr distillation (130°/0.25 mm) afforded the ketoester 28: 8.04 g, 70% yield from 26; mp 32-33°; TLC (Et_2O) 0.6; GC (260°) 0.65 min; NMR δ 1.7 (4H, m), 2.12 (3H, s, $COCH_3$), 2.5 (4H, m), 3.76 (3H, s, CO_2CH_3), 3.81 (3H, s, NCH_3), 5.88 (1H, d), 6.84 (1H, d). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.8; H, 8.1; N, 5.9. Found: C, 66.0; H, 8.2; N, 5.9.

6-(5-Methoxycarbonyl-1-methyl-2-pyrrolidinyl)-2-hexanol (29). The pyrrole ketoester (28, 7.84 g, 33.2 mmol) was dissolved in 50 mL methanol and a solution of sulfuric acid (5.6 ml, 100 mmol, 3.00 mol %) in 50 mL methanol was added. The solution was hydrogenated (40-50 psi) over 5% rhodium on alumina (7.84 g) for 44 hr, monitoring the progress of the reduction by UV. After removing the catalyst, the solvent was evaporated, water was added, the pH was adjusted to

1.5-2.0, and the aqueous solution was extracted 2 x with ether. The aqueous phase was then adjusted to pH 9.8 with saturated Na_2CO_3 and extracted 4 x with CH_2Cl_2. After drying and evaporation of the solvent, the crude product (7.5 g) was kugelrohr distilled (110°/0.15 mm) to afford pyrrolidine 29 as a clear oil (6.3 g, 78% yield): TLC ($CHCl_3/CH_3OH/NH_4$, 90/9.5/0.5) 0.5; GC (200°) 1.7 min; NMR δ 1.16 (3H, d, $HOCCH_3$), 1.1-2.3 (15H, m), 2.30 (3H, s, NCH_3), 2.96 (1H, br t), 3.69 (3H, s, CO_2CH_3). Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.2; H, 10.4; N, 5.8. Found: C, 64.1; H, 10.2; N, 5.7.

6-(5-Methoxycarbonyl-1-methyl-2-pyrrolidinyl)-2-hexanonate (30a). Jones reagent was prepared from CrO_3 (2.67 g, 26.7 mmol), sulfuric acid (2.3 ml, 41.5 mmol) and water (to 10.0 ml). Alcohol 29 (2.64 g, 10.9 mmol) was dissolved in 15 mL acetone and Jones reagent (4.0 ml, 10.7 mmol, 98 mol %) was added with mixing over 5 min and the exothermic reaction mixture was shaken for 5 min. Saturated aqueous sodium bicarbonate (40 ml) was added, the lower aqueous layer removed, and the upper acetone layer extracted once with CH_2Cl_2. The combined aqueous layers were extracted 4 x with CH_2Cl_2, the organic extract was dried and evaporated and the product purified by kugelrohr distillation (90-100°/0.15 mm): yield, 2.30 g, 88%; TLC ($CHCl_3/CH_3OH/NH_4OH$, 90/9.5/0.5) 0.7; GC (200°) 1.7 min, coinjects with 29; NMR δ 1.1-2.6 (13H, m), 2.11 (3H, s, $COCH_3$), 2.32 (3H, s, CO_2CH_3), 2.97 (1H, br t), 3.71 (3H, s, CO_2CH_3). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.7; H, 9.6; N, 5.8. Found: C, 64.7; H, 9.6; N, 5.8.

6-(5-Carboxy-1-methyl-2-pyrrolidinyl)-2-hexanone Hydrochloride (30b). The methyl ester (30a, 1.94 g, 8.05 mmol) was dissolved in 6M HCl (9.7 ml, 58 mmol, 720 mol %) and heated to 90° for 30 min under nitrogen. Excess HCl and water was removed (50°/2 mm) leaving a brown oil. Azeotropic removal of the remaining water afforded a semisolid which was dried to constant weight in vacuo over $CaSO_4$ and KOH: yield, 2.18 g, 103%; mp 130-133°C; TLC ($CHCl_3/CH_3OH/NH_4OH$, 80/19/1) 0.2-0.4; IR (nujol) 3350 (w), 2900, 1725, 1700 cm^{-1}; NMR δ 1.2-2.8 (12H, m), 2.18 (3H, s, $COCH_3$), 2.94 (3H, s, NCH_3), 3.3 (1H, m), 4.22 (1H, br t). Anal. Calcd for $C_{12}H_{22}NO_3Cl$: C, 54.6; H, 8.4; N, 5.3. Found: C, 54.9; H, 7.9; N, 5.2.

3,4-Dihydro-1-methyl-5-(5-oxohexyl)-2H-pyrrolium (31). Distilled $POCl_3$ (3.4 g, 22 mmol, 400 mol %) was added to the amino acid hydrochloride (30b, 1.40 g, 5.40 mmol) and the mixture heated to 105°. After 8 min, gas evolution subsided and most of the excess $POCl_3$ was rapidly removed with a stream of nitrogen, leaving the crude iminium salt 31: IR ($POCl_3$), 2930, 1710 (s), 1680 (w) cm^{-1}; NMR δ 1.3-3.5 (11H, m), 2.05 (3H, s, $COCH_3$), 3.56 (3H, br s, NCH_3), 4.3 (1H, m), 8.6 (1H, br s, N=CH).

6-(1-Methyl-2-pyrrolidinyl)-2-hexanol (32). A. The crude iminium salt 31 (from 31 mg 30b, 0.12 mmol) was dissolved in water (1 ml, pH = 0.5) and hydrogenated (50 psi, 1 hr) over PtO_2 (15 mg). Basification and extraction into CH_2Cl_2 afforded 32; yield, 21 mg, 97%.

B. Pyrrole ketone 26 (110 mg, 0.61 mmol) was dissolved in acetic acid (1 ml) and hydrogenated (45 psi, 40 hr) over PtO_2 (20 mg).

Partition between aq. alkali and CH_2Cl_2 afforded 32: yield, 85 mg, 75%; GC (200°) 0.65 min; NMR δ 1.18 (3H, d), 1.2-2.3 (16H, m), 2.29 (3H, s, NCH_3), 2.86 (1H, s, OH), 3.0 (2H, m), 3.67 (1H, t).

6-(1-Methyl-2-pyrrolidinyl)-2-hexanone (33). A. Iminium salt 31, hydrogenated as above, but at pH 1.5, afforded 33.

B. Jones oxidation of 32 following the procedure used to prepare 30a afforded 33 in 90% yield: GC (200°) 0.65 min; NMR δ 1.2-2.6 (13H, m), 2.12 (3H, s, $COCH_3$), 2.29 (3H, s, NCH_3), 3.0 (2H, m).

2-Acetyl-9-methyl-9-azabicyclo[4.2.1]nonane (34). A. The crude iminium salt 31 (5.40 mmol) was cooled to room temperature, dissolved in 30 mL methanol and heated to reflux for 16 hr. The mixture then was cooled, the methanol evaporated and replaced with water, the acidic aqueous solution was extracted twice with ether to remove trimethyl phosphate, then basified to pH 10 with sat. sodium carbonate and extracted 4 x with CH_2Cl_2. After drying and evaporation of solvent, the crude product (1.07 g) obtained was purified by kugelrohr distillation (60-65°/0.5 mm) to afford 34 as a clear oil: yield, 470 mg, 49%; TLC ($CHCl_3/CH_3OH/NH_4OH$, 80/19/1) 0.55 (variable, tailing); GC (200°) 0.75 min; IR 3400, 2920, 1705 cm^{-1}; (lit.[5] 1705 cm^{-1}); NMR δ 1.3-2.5 (11H, m), 2.12 (3H, s, $COCH_3$), 2.39 (3H, s, NCH_3), 3.3 (2H, m) [lit.[5] 2.09, 2.12 (singlets, ratio 1:2), 2.38, 2.48 (singlets, ratio 1:2]; MS m/e 181 (M^+, 32), 138 (M^+-$COCH_3$, 30), 82 (100). Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.9; H, 10.6; N, 7.7. Found: C, 72.7; H, 10.5; N, 7.6.

The product was stored at 0° under nitrogen for several weeks

with no decomposition. Contrary to a previous observation[5] NMR revealed only one epimer, and no epimerization was observed after 3 hr at pH 10. The hydrochloride of 34 was an extremely hygroscopic white powder; mp 121-125°C (lit.[5] mp 152-155°); single enantiomer, NMR δ 2.22 (3H, s, $COCH_3$), 2.90 (3H, s, NCH_3) [lit. δ 2.22 (3H, s), 2.91 (3H, s)]; LD_{50} > 25 mg/kg (ip, mouse).

B. Ester 21a (6.6 mg, 0.0335 mmol) was hydrolyzed in 0.1M aqueous LiOH (105 mol %) for 1 h, then dried (60°/1 mm/18 h) and pulverized affording lithium salt 21b. This was suspended in DME (0.5 ml) and treated with CH_3Li using the procedure employed to prepare 26. The product was purified by kugelrohr distillation (3.4 mg, 56% yield) and was identical with 34 prepared above.

2-Acetyl-9-(2,2,2-trichloroethoxycarbonyl)-9-azabicyclo[4.2.1]-nonane (35a). Bicyclic ketone 34 (100 mg, 0.55 mmol) was dissolved in anhydrous benzene (1 mL), 2,2,2-trichloroethoxycarbonyl chloride (0.10 mL, 0.726 mmol, 130 mol %) was added, and the solution was refluxed for 20 hr. The benzene was evaporated and replaced with ether and the ethereal solution was applied to silica gel (200 mg), eluting with ethyl acetate. Excess 2,2,2-trichlorethoxycarbonyl chloride was evaporated, leaving reasonably pure 35a as a yellow oil (153 mg, 81% yield): TLC (Et_2O/EtOAc, 99/1) 0.6 (minor), 0.65 (major); GC (270°) 1.1 (80%), 1.25 (15%), 1.8 (5%) min; NMR δ 1.2-2.5 (11H, m), 2.15 (3H, s, $COCH_3$), 4.2-4.8 (2H, m), 4.78 (2H, s, CH_2CCl_3) and 2.79 (s, NCH_3 in side product).

2-Acetyl-9-azabicyclo[4.2.1]nonane (35b). The trichloroethyl carbamate (35a, 69 mg, 0.20 mmol) was dissolved in glacial acetic acid/water, 9/1 (0.7 ml) and zinc dust (100 mg, 1.5 mmol,

750 mol %) was added portionwise. After 2.5 h, the zinc was removed and the solvent evaporated, leaving a residue which was dissolved in CH_2Cl_2 and shaken with saturated sodium carbonate. The product was rapidly extracted from the CH_2Cl_2 layer with 0.1M HCl, and the aqueous acid evaporated to afford the hydrochloride salt of 35b as a light orange oil (29 mg, 71% yield): TLC ($CHCl_3/CH_3OH/NH_4OH$, 80/19/1), 0.3-0.4; NMR δ 1.5-3.3 (11H, m), 2.23 (3H, s, $COCH_3$), 4.2 (2H, m); LD_{50} = 2.5 mg/kg (ip, mouse).

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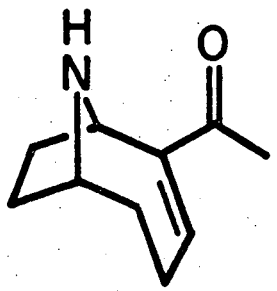
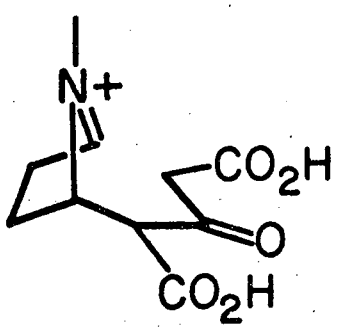
Table I. Effect of pH on Stability of Iminium Salt 16 and Its Cyclization to Bicyclic Malonate 18 at 20°C.

pH	Yield 16	Unreacted 18[a]
3.0	0%	100%
6.0	0.5%	80%
6.6	0.5%	70%
7.5	4%	55%
8.0	7%	50%
8.8	1%	2%

[a]Quantity of 16 and 18 determined after 5 min of reaction. The amount of 16 was determined by reduction to 17.



1, Anatoxin-a



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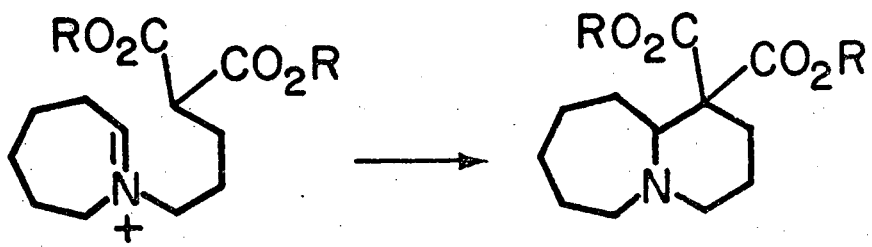
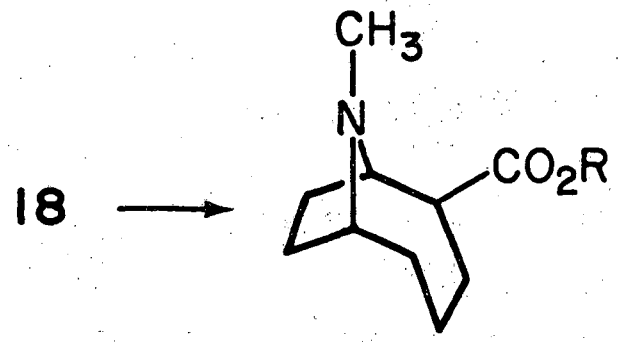
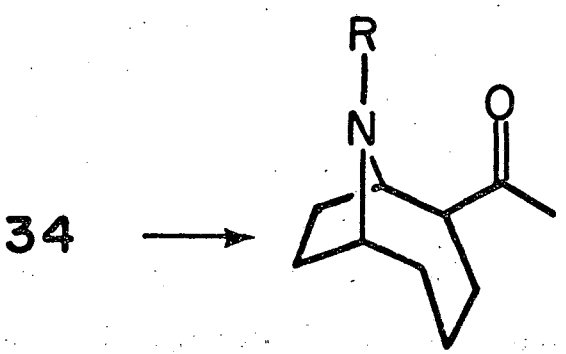


19 20

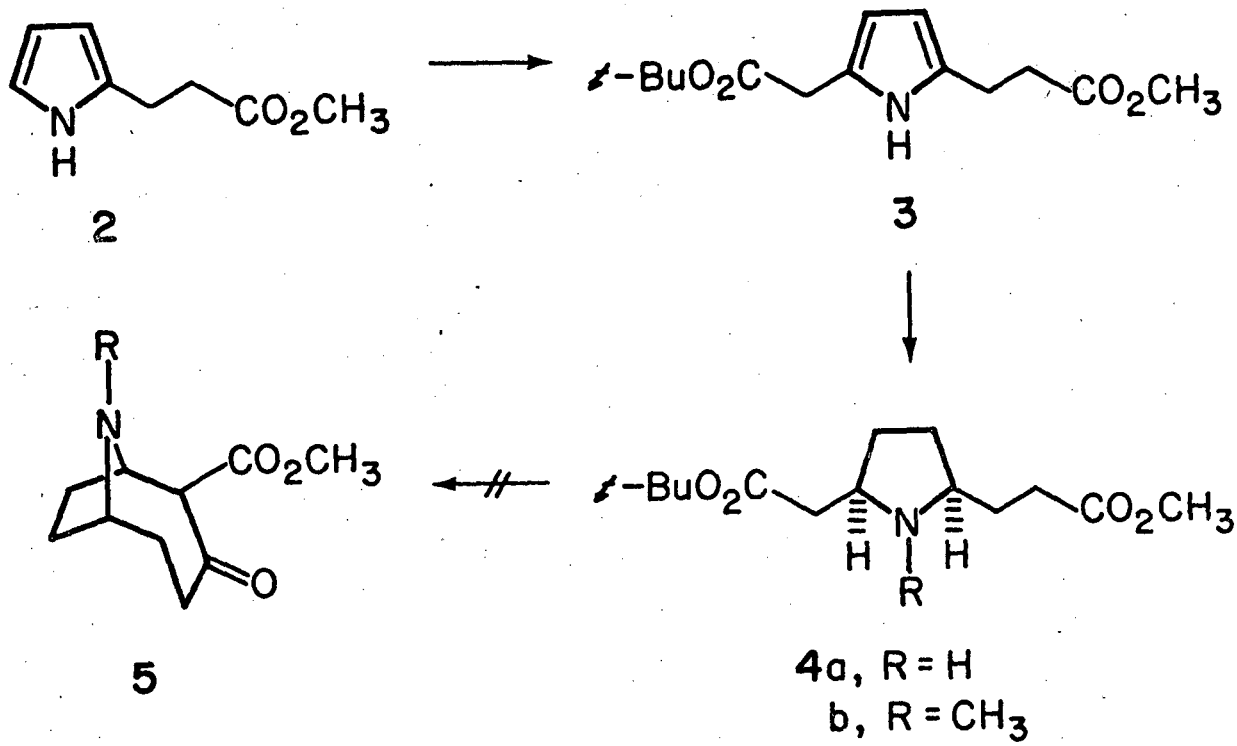


21a, R = CH_3
b, R = Li

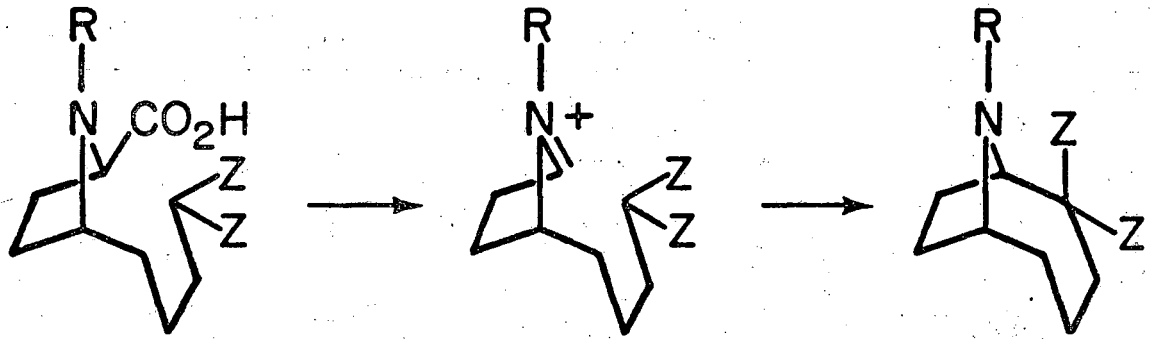


35a, R = $CO_2CH_2CCl_3$
b, R = H

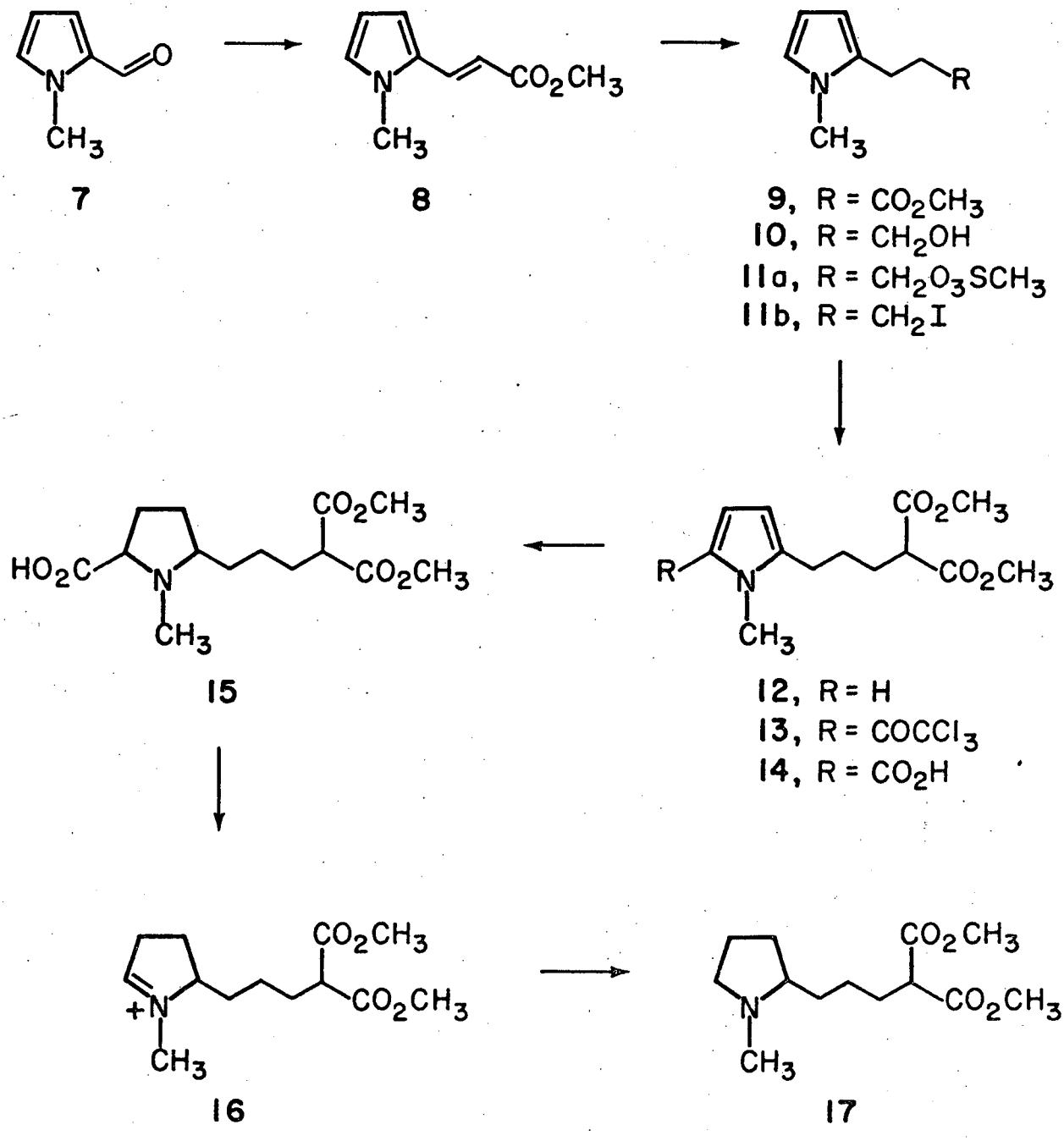
Scheme I


CO2CH3
N
H
2
t-BuO2C
CO2CH3
N
H
3
R
N
CO2CH3
O
5
t-BuO2C
CO2CH3
N
H
H
R
4a, R = H
b, R = CH3

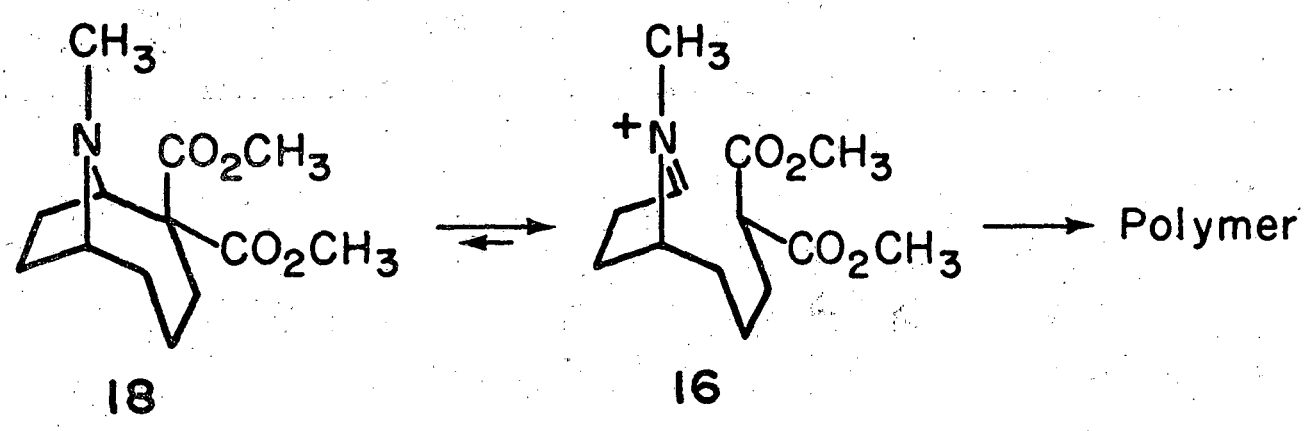
Scheme II



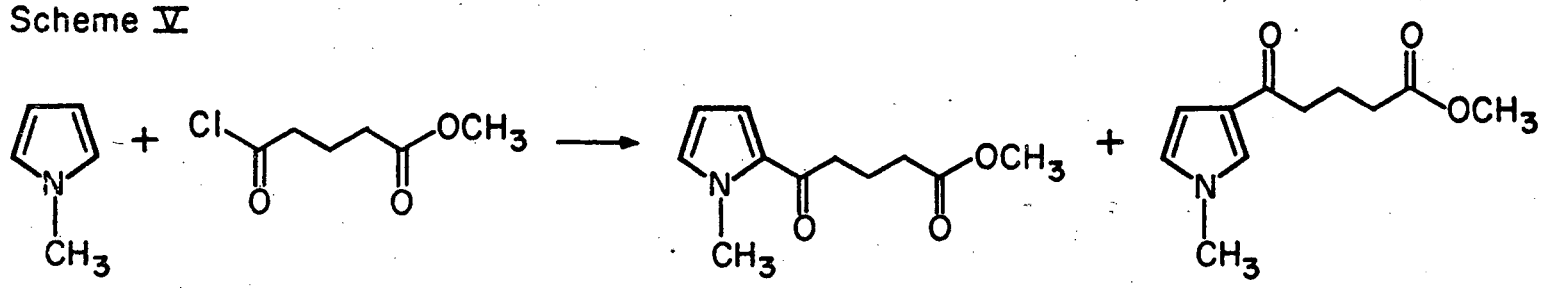
Scheme III


7
8
9, R = CO2CH3
10, R = CH2OH
11a, R = CH2O3SCH3
11b, R = CH2I
12, R = H
13, R = COCCl3
14, R = CO2H
15
16
17

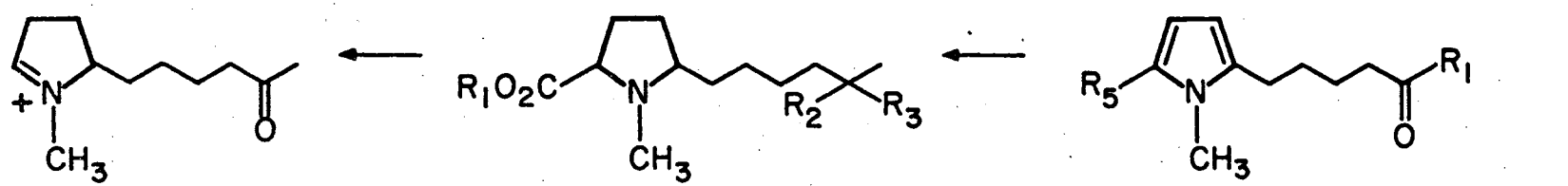
Scheme IV



Scheme V



22 23 24



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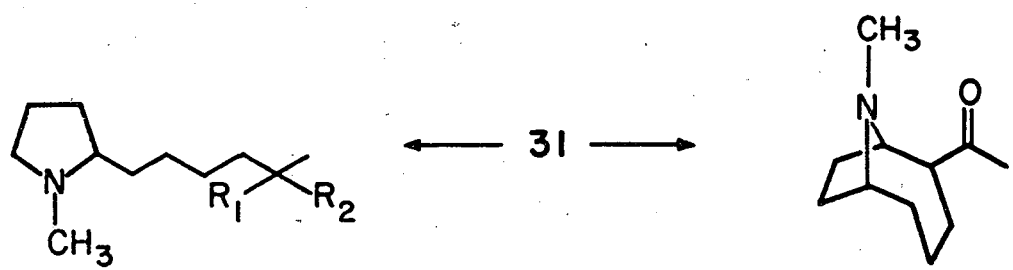
29, $R_1 = CH_3$; $R_2 = OH$; $R_3 = H$
30a, $R_1 = CH_3$; $R_2, R_3 = O$
30b, $R_1 = H$; $R_2, R_3 = O$

25, $R_5 = H$; $R_1 = OH$
26, $R_5 = H$; $R_1 = CH_3$
27, $R_5 = COCCl_3$; $R_1 = CH_3$
28, $R_5 = CO_2CH_3$; $R_1 = CH_3$



32, $R_1 = OH$, $R_2 = H$
33, $R_1, R_2 = O$

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