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

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Hans A. Bates and Henry Rapoport

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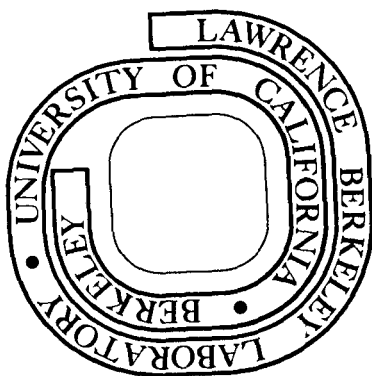
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1 THE SYNTHESIS OF ANATOXIN-a VIA INTRAMOLECULAR  
2 CYCLIZATION OF IMINIUM SALTS

3  
4 Hans A. Bates and Henry Rapoport\*

5  
6 Contribution from the Department of Chemistry and Lawrence  
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8

9  
10  
11 Abstract: Anatoxin-a (1) has been synthesized by exploiting intra-  
12 molecular cyclization between an iminium salt and a nucleophilic  
13 carbon to construct the 9-azabicyclo[4.2.1]nonane ring system.  
14 Cyclization of malonate iminium salt 16 at alkaline pH afforded  
15 a low yield of bicyclic malonate 18 due to an unfavorable  
16 equilibrium constant and lability of the iminium salt in base.  
17 In contrast, cyclization of keto-iminium salt 31 afforded a good  
18 yield of bicyclic ketone 34 in acidic methanol. Dihydropyrrolium  
19 salts 16 and 31 were generated quantitatively by decarbonylation  
20 of substituted N-methylprolines 15 and 30b, obtained by reduction  
21 of the corresponding pyrroles.  
22  
23  
24  
25  
26  
27

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

[Structure] 1  
8 In contrast to the many examples of the 8-azabicyclo[3.2.1]-  
9 octane ring system found in the diverse and widely distributed  
10 atropine alkaloids, anatoxin-a is the only naturally occurring  
11 representative of the homologous 9-azabicyclo[4.2.1]nonane series.  
12 Only two syntheses of this class of compounds have been reported,  
13 and both utilized ring expansion of the more readily available  
14 8-azabicyclo[3.2.1]octanes. Thus 9-azabicyclo[4.2.1]nonan-3-one  
15 was first prepared by Tiffeneau ring expansion from tropinone.<sup>4</sup>  
16 More recently, a partial syntheses of anatoxin-a via ring expansion  
17 from cocaine was reported.<sup>5</sup>

18 We chose to examine a direct and potentially broader approach  
19 to anatoxin-a involving closure of the eight-membered carbon ring  
20 (seven-membered, counting through nitrogen) into an appropriately  
21 substituted pyrrolidine. Initially, we considered ring closure via  
22 a Dieckmann cyclization of the appropriate pyrrolidine-2,5-diester  
23 4b as shown in Scheme I. However, this was unsuccessful, as might  
24 have been anticipated from the low yield of the analogous Dieckmann  
25 cyclization leading to tropinone-2-carboxylate<sup>6,7</sup> and the known  
26 difficulty of extending this reaction to medium-sized rings.

Scheme] I  
27 This communication describes the successful synthesis of

1 anatoxin-a via intramolecular cyclization between an iminium salt  
2 and a carbon atom bearing electron-withdrawing substituents as shown  
3 in the generalized Scheme II. Similar cyclizations have been  
4 successfully employed for the closure of relatively unstrained 5-  
fn 8,9 5 and 6-membered rings, and occasionally bridged systems,<sup>8,9</sup> and the  
6 facility with which these cyclizations occur encouraged us to pursue  
7 this approach toward the more challenging strained and bridged 9-  
8 azabicyclo[4.2.1]nonane skeleton of anatoxin-a. The major encumbrance  
9 to synthetic utilization of iminium salts, the absence of a versatile  
10 method for their generation, was recently surmounted with the  
11 introduction of a high-yield, regiospecific method based on decar-  
fn 10 12 bonylation of  $\alpha$ -amino acids,<sup>10</sup> and this approach was exploited in  
13 the present investigation as shown in Scheme II. The conditions  
14 and substituents necessary for effecting the key cyclization  
15 reaction were examined in detail.

[Scheme II.]

### 17 Results and Discussion

18 Prior to examining intramolecular cyclization of iminium  
19 salts for the synthesis of anatoxin-a, we attempted to extend the  
20 scope of the Dieckmann cyclization, successfully utilized in the  
21 synthesis of tropinone-2-carboxylate,<sup>6,7</sup> to the preparation of  
22 homologous  $\beta$ -keto ester 5. Unsymmetrical t-butyl methyl diester  
23 4b was selected as a precursor in order to direct the cyclization  
fn 11 24 in the desired manner.<sup>11</sup> Thus (Scheme I) methyl 3-(2-pyrrolyl)-  
25 propanoate (2), obtained from pyrrole-2-carboxaldehyde by condensa-  
26 tion with hydrogen methyl malonate followed by hydrogenation, was  
27 treated with t-butyl diazoacetate in the presence of a copper

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

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

20 1-Methylpyrrole-2-carboxaldehyde (7) was condensed with hydrogen methyl  
21 malonate to afford acrylate 8 (a Wittig reaction was more cumbersome  
22 and gave a lower yield) which was catalytically reduced to propanoate  
23 9 over Pd/C, and further reduced to alcohol 10 with LiAlH<sub>4</sub>. Con-  
24 verting alcohol 10 into a leaving group capable of displacement by  
25 dimethyl malonate anion proved to be unexpectedly difficult.  
26 Formation of the bromide or chloride with numerous reagents gave  
27 low yields of product, due to sensitivity of the electron-rich

En 12

[trunc-]  
ure 6]Scheme I  
III

1 pyrrole to oxidation and acid-catalyzed polymerization. Even the  
2 best conditions,  $\text{PBr}_3$ /pyridine or  $\text{CBr}_4$ /triphenylphosphine, gave  
3 ~20% yield. The methanesulfonate 11a was easily prepared as was the  
4 toluenesulfonate derivative, but these gave only low yields of 12  
5 when treated with dimethyl malonate anion. Therefore the methane-  
6 sulfonate 11a was converted to iodide 11b which gave an excellent  
7 yield of malonate 12 upon displacement with sodio dimethyl malonate.

n 13

8 Pyrrole 12 was treated with trichloroacetyl chloride<sup>13</sup> to  
9 afford the 5-trichloroacetylpyrrole 13. The trichloroacetyl group  
10 was then hydrolyzed to pyrrole acid 14 with a slight excess of NaOH  
11 in a mixture of water and acetone. Kinetic studies demonstrated  
12 that no appreciable hydrolysis of the malonate methyl ester would  
13 occur, since hydrolysis of the trichloroacetyl function is one  
14 hundred times faster. Hydrogenation of pyrrole 14 to pyrrolidine  
15 15 was best accomplished in methanol with rhodium/alumina catalyst.  
16 Platinum was not an effective catalyst in methanol, and in acetic  
17 acid substantial decarboxylation of 14 accompanied hydrogenation.  
18 Decarbonylation of amino acid 15 with  $\text{POCl}_3$  at  $105^\circ$ <sup>10</sup> afforded a  
19 quantitative yield of iminium salt 16, which was not isolated, but  
20 was completely characterized spectroscopically and by catalytic  
21 reduction to pyrrolidine 17.

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



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

9 Longer reaction times and higher temperatures did not increase  
 10 the yield of 18, but unexpectedly, had just the opposite effect.  
 11 This observation suggested that the cyclization was reversible.  
 12 Indeed, when the isolated bicyclic malonate 18 was placed in  
 13 water at pH 7 or 10, it decomposed with a half-life of 10 and  
 14 5 minutes, respectively. Furthermore, in aqueous acid (pH 1-3) 18  
 15 formed iminium salt 16 in nearly quantitative yield with a half-  
 16 life of 2 hours. In summary, as shown in Scheme IV, the low yield  
 17 of 18 is due to an equilibrium very unfavorable toward its formation  
 18 as well as irreversible polymerization which decimates the product  
 19 at alkaline pH. By rapidly extracting 18 into dichloromethane or  
 20 chloroform immediately after adding base to 16, it was possible to  
 21 trap more of the product, and yields of 20 to 25% were obtained.

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

[Scheme]  
 IV

[Struc-  
 tures  
 19,20]

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

fn 16

12 In order to ascertain whether the bicyclic ketone 34 actually  
 13 exhibited the predicted increased stability over bicyclic malonate  
 14 18, a sample of 34 was prepared from 18. Thus the bicyclic malonate  
 15 18 was hydrolyzed and decarboxylated in 6M HCl, then re-esterified  
 16 to afford bicyclic ester 21a. The ester 21a was hydrolyzed to  
 17 lithium salt 21b with LiOH and subsequently treated with methyl  
 18 lithium, leading to the desired bicyclic ketone 34. In accord with  
 19 prediction, 34 was found to be two orders of magnitude more stable  
 20 than 18. The half-life of 34 is 5 h at pH 10 (compared to 5 min for  
 21 18) and no decomposition could be observed in acid at 20°. Thus we  
 22 proceeded to prepare keto iminium salt 31, confident that it would  
 23 cyclize to bicyclic ketone 34.

[Struc-  
tures  
21a,b]

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

[Scheme  
V]

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

8 Wolff-Kishner reduction of ketone 23 afforded 5-(1-methyl-2-  
9 pyrrolyl)pentanoic acid (25) in quantitative yield. The lithium  
10 salt of 25 was treated with a slight excess of methyllithium,  
11 producing ketone 26, and acylation with trichloroacetyl chloride  
12 afforded 27 which reacted with methoxide to give methyl ester 28.  
13 Catalytic reduction of this pyrrole to pyrrolidine 29 was  
14 accomplished using rhodium-alumina in acidic methanol. The ketone  
15 functionality was restored by oxidizing alcohol 29 with Jones  
16 reagent to ketone 30a. Protecting the ketone in 28 as its dimethyl  
17 ketal prior to hydrogenation was less satisfactory. The keto methyl  
18 ester 30a was then hydrolyzed with aqueous HCl, providing the  
19 hydrochloride of keto amino acid 30b which was decarbonylated with  
20 POCl<sub>3</sub> to afford iminium salt 31. Catalytic reduction to pyrrolidines  
21 32 and 33 demonstrated that the yield of 31 was quantitative.

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

1 Catalytic reduction of the reaction mixture demonstrated that after  
2 14 and 42 h of reflux, 43% and 15%, respectively, of the original  
3 iminium salt remained unreacted. These results indicate that, again,  
4 a reversible equilibrium and a non-reversible polymerization of  
5 the iminium salt occur in analogy to Scheme IV. However, the  
6 equilibrium constant for  $\underline{31} \rightarrow \underline{34}$  is approximately 3 and the poly-  
7 merization is slow, whereas the equilibrium constant for  $\underline{16} \rightarrow \underline{18}$   
8 is less than 0.2 and polymerization is rapid at the alkaline pH  
9 requisite for cyclization.

10 The successful synthesis of bicyclic ketone  $\underline{34}$  formally  
11 competes the synthesis of anatoxin-a (1), since  $\underline{34}$ , prepared by  
12 ring expansion from cocaine, has been converted to anatoxin-a.<sup>5</sup>  
13 Contrary to the previous observations, however,  $\underline{34}$  prepared  
14 from  $\underline{31}$  or  $\underline{18}$  was totally homogeneous, NMR revealed only one epimer,  
15 and no epimerization occurred, suggesting that perhaps the  $\underline{34}$   
16 obtained previously may have been impure.

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

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

[Struc-  
tures  
35a,b]

## 1 Experimental Section

2       General Procedures. Gas chromatography was performed  
3 using a Hewlett-Packard 402 gas chromatograph equipped with a 6'  
4 5% SE-30 column at 40 psi He. Pre-coated EM Reagent silica gel  
5 60 F-254 TLC plates were used. The pyrroles were visualized by  
6 short wave UV light and by spraying with a reagent prepared from  
7  $\text{Ce}(\text{SO}_4)_2 \cdot 2 \text{H}_2\text{O}$  (2.1 g), concentrated sulfuric acid (2.8 ml) and  
8 water (100 ml) followed by heating. Other compounds were visualized  
9 by spraying with a 10% solution of phosphomolybdic acid in 95%  
10 ethanol followed by heating. NMR spectra were recorded with a  
11 Varian T-60 spectrometer in  $\text{CDCl}_3$  (TMS as internal standard) or  
12 in  $\text{D}_2\text{O}$  (sodium 3-(trimethylsilyl)propanesulfonate (DDS) as internal  
13 standard) unless otherwise specified. IR spectra were recorded as  
14 thin films. Reaction temperatures were bath temperatures unless  
15 internal is specified.(i.t.). Reactions were carried out under a  
16 nitrogen atmosphere, using magnetic stirring. Organic solutions  
17 were dried over anhydrous magnesium sulfate, and solvents were  
18 evaporated in vacuo using a Berkeley rotary evaporator. Elemental  
19 analyses were performed by the Analytical Laboratory, Department of  
20 Chemistry, University of California, Berkeley.

21       Hydrogen Methyl Malonate was prepared by a modification of the  
22 procedure used to prepare hydrogen ethyl malonate.<sup>18</sup> Methanolic  
23 KOH (179 g, 3.2 mol, in 2.1L) was added to methanolic dimethyl  
24 malonate (423 g, 3.2 mol, in 2.1L) over 1 h. After 18 h, the  
25 potassium salt (375 g, 2.4 mol) was pptd. by cooling ( $-13^\circ$ ) and con-  
26 centrating the mixture, then washed with ether. The aqueous  
27 potassium salt (375 g in 375 mL) was slowly (1 h) acidified (pH 1.5)

1 with conc HCl (2.4 mmol) at i.t. 5-10° and the product was extracted  
2 from the aqueous solution and the KCl ppt with ether to give 232 g,  
3 62% yield.

4 Methyl 3-(2-Pyrrolyl)propanoate (2). Pyrrole-2-carboxaldehyde  
5 (81.2 g, 0.855 mol) was condensed with hydrogen methyl malonate  
6 (201 g, 1.71 mol, 200 mol %) in pyridine (425 mL) and piperidine (10 mL)  
7 at i.t. 50-60° for 42 h and 70-80° for 28 h. Ether (1.8L) was added  
8 and the pyridine and piperidine extracted into 1.8 M HCl (2x2 L).  
9 The organic phase was washed with aq. Na<sub>2</sub>CO<sub>3</sub>, dried, and the ether  
10 was evaporated, leaving crude dark purple methyl (E)-β-(2-pyrrolyl)-  
11 acrylate (97 g) contaminated with dimethyl 3-(2-pyrrolyl)glutarate.  
12 The crude product was dissolved in methanol (1 L) and hydrogenated  
13 (50 psi, 6 h) over 10% Pd/C (9 g). Removal of catalyst and  
14 evaporation of solvent followed by distillation (75°/0.3 mm)  
15 afforded the product 2 as a clear liquid (58.5 g, 45% yield):  
fn 19 mp 8-11° (lit.<sup>19</sup> bp 75°/0.3 mm); NMR δ 2.70 (4H, m), 3.64 (3H, s),  
16 5.74 (1H, m), 5.89 (1H, m), 6.46 (1H, m).  
17

18 Methyl 3-(5-t-Butoxycarbonylmethyl-2-pyrrolyl)propanoate (3).  
fn 20 t-Butyl diazoacetate<sup>20</sup> (25.9 g, 182 mmol, 128 mol %) was added over  
19 3 h to a mixture of methyl 3-(2-pyrrolyl)propanoate (2) (21.7 g,  
20 142 mmol) and copper powder (1.35 g) in benzene (45 ml) at i.t. 70°.  
21 After 1 h more, the solvent was evaporated, starting material (5.2 g)  
22 removed (72°/0.2 mm) and the product kugelrohr distilled (110°,  
23 0.2 mm) to give a yield of 23.1 g, 61% based on 2 added, 80% based  
24 on 2 consumed: NMR (CCl<sub>4</sub>) δ 1.45 (9H, s), 2.71 (4H, m), 3.46 (2H, s),  
25 3.68 (3H, s), 5.72 (2H, m), 8.9 (1H, br). Anal. Calcd. for  
26 C<sub>14</sub>H<sub>21</sub>NO<sub>4</sub>: C, 62.9; H, 7.9; N, 5.2. Found: C, 63.1; H, 7.8; N, 5.3.  
27

1 Methyl 3-(5-t-Butoxycarbonylmethyl-2-pyrrolidinyl)propanoate

2 (4a). The pyrrole 3 was hydrogenated (35 psi, 5h) over Pt in  
3 acetic acid. After isolation by partition between aqueous acid/  
4 CH<sub>2</sub>Cl<sub>2</sub> and aq. alkali/CH<sub>2</sub>Cl<sub>2</sub>, the product was kugelrohr distilled  
5 (90-100°/0.1 mm) in 78% yield: NMR (CCl<sub>4</sub>) δ 1.44 (9h, s),  
6 1.0-2.5 (10H, m), 3.2 (2H, m), 3.68 (3H, s); MS m/e 271 (0.4, M<sup>+</sup>),  
7 214 (17); Anal. Calcd. for C<sub>14</sub>H<sub>25</sub>NO<sub>4</sub>: C, 62.0; H, 9.3; N, 5.2.  
8 Found: C, 61.9; H, 9.0; N, 5.1.

9 Methyl 3-(5-t-Butoxycarbonylmethyl-1-methyl-2-pyrrolidinyl)-  
10 propanoate (4b). Pyrrolidine 4a (3.51 g, 13.0 mmol) was dissolved  
11 in CH<sub>3</sub>OH (40 mL) and aqueous formaldehyde (62 mmol, 450 mol %) was  
12 added. The mixture was hydrogenated (30 psi, 19 hr) over 10% Pd/C  
13 (500 mg), the catalyst was removed and the solvent evaporated.  
14 The product (3.12 g, 84%) was kugelrohr distilled (110°/0.1 mm):  
15 NMR (CCl<sub>4</sub>) δ 1.41 (9H, s), 1.3-2.8 (12H, m), 2.21 (3H, s), 3.58  
16 (3H, s); MS m/e 285 (1.8, M<sup>+</sup>), 198 (50), 142 (100); Anal. Calcd.  
17 for C<sub>15</sub>H<sub>27</sub>NO<sub>4</sub>: C, 63.2; H, 8.5; N, 4.9. Found: C, 63.6; H, 9.5;  
18 N, 5.0.

19 Attempted Dieckmann Cyclization of 4b. The starting material,  
20 t-butyl methyl ester 4b, was added to a mixture of toluene, t-butanol  
21 (10 mol %) and KH (110 mol %) and refluxed beneath 4A molecular  
22 sieves over 28 h. After an additional 24 h of reflux, the reaction  
23 was quenched, affording only starting material (55%) and none of  
24 the desired β-keto ester 5 (MS, FeCl<sub>3</sub>). Under the same conditions,  
25 methyl t-butyl suberate cyclized to the t-butyl β-ketoester in 55%  
26 yield.  
27

fn 21 1 Methyl (E)- $\beta$ -(1-Methyl-2-pyrrolyl)acrylate (8). A mixture of  
2 1-methylpyrrole-2-carboxaldehyde<sup>21</sup> (7, 101 g, 927 mmol), hydrogen  
3 methyl malonate (125 g, 1 mol, 114 mol %), pyridine (400 mL) and  
4 piperidine (18.5 mL, 187 mmol, 20 mol %) were stirred under N<sub>2</sub> at  
5 i.t. 70° for 35 h. Evolution of CO<sub>2</sub> was essentially complete after  
6 25 h. Solvent was evaporated, followed by drying at 50°/5 mm/2 h.  
7 Distillation afforded some recovered aldehyde (80°/2 mm) followed  
8 by the acrylate 8 (120°/2 mm): 101 g, 77% yield based on starting  
9 material consumed; GC (180°) 2.5 min; NMR  $\delta$  3.66 (3H, s, NCH<sub>3</sub>),  
10 3.71 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 6.03 (1H, d, J=16, C=CH), 6.1 (1H, m), 6.6  
11 (1H, m), 7.50 (1H, d, J=16 C=CH); MS m/e 165 (76, M<sup>+</sup>), 134 (100,  
12 M<sup>+</sup>-CH<sub>3</sub>O). Anal. Calcd. for C<sub>9</sub>H<sub>11</sub>NO<sub>2</sub>: C, 65.4; H, 6.7; N, 8.5.  
13 Found: C, 65.2; H, 6.7; N, 8.4.

14 Methyl 3-(1-Methyl-2-pyrrolyl)propanoate (9) was prepared by  
15 hydrogenating methyl (E)- $\beta$ -(1-methyl-2-pyrrolyl)acrylate (8, 10 g)  
16 in methanol over 10% Pd/C (1 g in 100 mL) for 2 h at 50 psi.  
17 Removal of the catalyst and evaporation of the CH<sub>3</sub>OH left the  
18 product: 9.5 g, 94%; bp 75-80°/2.5 mm by kugelrohr distillation;  
19 GC (180°) 1.0 min; NMR  $\delta$  2.74 (4H, m, CH<sub>2</sub>CH<sub>2</sub>), 3.53 (3H, s,  
20 NCH<sub>3</sub>), 3.69 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 5.9 (1H, m), 6.05 (1H, t), 6.55 (1H,  
21 t); MS m/e 167 (18, M<sup>+</sup>), 94(100). Anal. Calcd for C<sub>9</sub>H<sub>13</sub>NO<sub>2</sub>:  
22 C, 64.7; H, 7.8; N, 8.4. Found: C, 64.5; H, 7.9; N, 8.3.

23 3-(1-Methyl-2-pyrrolyl)propanol (10). Crude methyl propanoate  
24 (9, 8.9 g, 53.2 mmol) was dissolved in 75 mL dry ether and  
25 filtered and the filtrate was added to a suspension of LiAlH<sub>4</sub>  
26 (2.5 g, 64 mmol, 120 mol %) in 75 mL ether over 1/2 h. After  
27 stirring 2 hr more at 20°, to the reaction mixture was added 9 mL



1 H<sub>2</sub>O and 4 mL 10% NaOH, removing the precipitate, then evaporating  
2 the solvent to afford the propanol 10: 6.7 g, 89% yield; GC (150°)  
3 0.9 min, (200°) 0.25 min; bp 80-120°/1.1 mm by kugelrohr distil-  
4 lation; NMR δ 1.8 (1H, br, OH), 1.85 (2H, m), 2.65 (2H, br t, J=7),  
5 3.54 (3H, s, NCH<sub>3</sub>), 3.70 (2H, t, J=6), 5.9 (1H, m), 6.02 (1H, t),  
6 6.52 (1H, t); MS m/e 139 (14, M<sup>+</sup>), 94(100). Anal. Calcd for  
7 C<sub>8</sub>H<sub>13</sub>NO: C, 69.0; H, 9.4; N, 10.1. Found: C, 68.9; H, 9.3;  
8 N, 10.1.

9 3-(1-Methyl-2-pyrrolyl)propanol Methanesulfonate (11a). Crude  
10 propanol 10 (51 g, 367 mmol) was dissolved in 500 mL CH<sub>2</sub>Cl<sub>2</sub> and  
11 triethylamine (80 mL, 570 mmol, 155 mol %) was added. After cooling  
12 to 0°, methanesulfonyl chloride (37 mL, 48 mmol, 130 mol %, dis-  
13 tilled) was added over 20 min. After 1 h additional stirring  
14 at 0°, the mixture was washed with satd. NaCl, satd Na<sub>2</sub>CO<sub>3</sub>, satd.  
15 NaCl (100 mL each), and dried. The solvent was removed to afford  
16 the product as an orange oil (81 g, 102% crude yield): bp 159°/1.0  
17 mm by kugelrohr distillation; NMR δ 2.1 (2H, m), 2.7 (2H, br t),  
18 2.97 (3H, s, OSO<sub>2</sub>CH<sub>3</sub>), 3.53 (3H, s, NCH<sub>3</sub>), 4.29 (2H, t, J=7),  
19 5.85 (1H, m), 6.02 (1H, t), 6.52 (1H, t); MS m/e 217 (7, M<sup>+</sup>), 94  
20 (100). Anal. Calcd for C<sub>9</sub>H<sub>15</sub>NO<sub>3</sub>S: C, 49.8; H, 7.0; N, 6.5.  
21 Found: C, 49.5; H, 7.0; N, 6.5.

22 2-(3-Iodopropyl)-1-methylpyrrole (11b). The crude methane-  
23 sulfonate (11a, 81 g, 373 mmol) was dissolved in 550 mL absolute  
24 ethanol and sodium iodide (112 g, 750 mmol, 200 mol %) was added.  
25 A mildly exothermic reaction ensued. After stirring 20 h at 40°,  
26 the ethanol was evaporated, the residue was partitioned between ether  
27 and water, and the organic phase evaporated then kugelrohr distilled

1 to afford the iodide as a nearly colorless liquid: 51.5 g, 56%  
2 yield; GC (200°) 0.55 min; NMR  $\delta$  2.15 (2H, m), 2.65 (2H, br t),  
3 3.22 (2H, t, J=7), 3.52 (3H, s, NCH<sub>3</sub>), 5.85 (1H, m), 5.97 (1H, t),  
4 6.47 (1H, t); MS m/e 249 (16, M<sup>+</sup>), 94(100). Anal. Calcd. for  
5 C<sub>8</sub>H<sub>12</sub>NI: C, 38.6; H, 4.9; N, 5.6. Found: C, 38.4; H, 4.9; N, 5.6.

6 Methyl 2-Methoxycarbonyl-5-(1-methyl-2-pyrrolyl)pentanoate (12).

7 Sodium (9.5 g, 413 mmol, 187 mol %) was dissolved in 250 mL  
8 methanol at 0°. Dimethyl malonate (50.5 mL, 442 mmol, 200 mol %)  
9 was added and the solution stirred at room temperature 30 min.  
10 The propyl iodide (11b, 55 g, 221 mmol) in 150 mL methanol was  
11 added and the solution refluxed 1/2 h, then cooled to 0°, a 1.0M  
12 methanolic H<sub>2</sub>SO<sub>4</sub> solution was added to pH 8, the methanol was  
13 evaporated and replaced with ether, and after extraction with  
14 water, the excess dimethyl malonate was distilled (50°/0.2 mm)  
15 leaving the pyrrole malonate 12 (53.7 g, 96% yield), purified by  
16 kugelrohr distillation: GC (200°) 2 min; TLC (Et<sub>2</sub>O) 0.65 (Et<sub>2</sub>O/  
17 pet ether 1/1) 0.45; NMR  $\delta$  1.5-2.2 (4H, m), 2.55 (2H, br t),  
18 3.40 (1H, m), 3.50 (3H, s, NCH<sub>3</sub>), 3.73 (6H, s, CO<sub>2</sub>CH<sub>3</sub>), 5.85 (1H, m),  
19 5.99 (1H, t), 6.50 (1H, t); MS m/e 253 (9, M<sup>+</sup>), 94 (100). Anal.  
20 Calcd. for C<sub>13</sub>H<sub>19</sub>NO<sub>4</sub>: C, 61.6; H, 7.6; N, 5.5. Found: C, 61.5;  
21 H, 7.6; N, 5.5.

22 Methyl 2-Methoxycarbonyl-5-(1-methyl-5-trichloroacetyl-2-  
23 pyrrolyl)pentanoate (13). A modification of the previous method<sup>13</sup>  
24 was used. Potassium carbonate (ground finely then dried at 350°,  
25 12 h, 58.5 g, 424 mmol, 200 mol %) was suspended in 500 mL ether  
26 and trichloroacetyl chloride (29 mL, 260 mmol, 125 mol %) added,  
27 followed by the pyrrole malonate (12, 53.7 g, 212 mmol) in 100 mL

1 ether over 10 min. The mixture was stirred 2 h then filtered,  
2 extracted with satd. sodium bicarbonate and dried to afford the  
3 trichloroacetyl derivative 13: 82.5 g, 97.5% yield; mp 77-78°  
4 from pet ether; UV (CH<sub>3</sub>OH) 322 nm ( $\epsilon$  15,000); TLC (Et<sub>2</sub>O/pet ether  
5 1/1) 0.38; NMR  $\delta$  1.5-2.2 (4H, m), 2.62 (2H, br t), 3.37 (1H, t),  
6 3.71 (6H, s, CO<sub>2</sub>CH<sub>3</sub>), 3.81 (3H, s, NCH<sub>3</sub>), 5.99 (1H, d, J=4,5),  
7 7.31 (1H, d, J=4,5); MS m/e 397 (3, M<sup>+</sup>), 399 (3, M<sup>+</sup>), 401 (1, M<sup>+</sup>),  
8 280 (100, M<sup>+</sup>-CCl<sub>3</sub>).

9 Methyl 2-Methoxycarbonyl-5-(5-carboxy-1-methyl-2-pyrrolyl)-  
10 pentanoate (14). The trichloroacetyl pyrrole (13, 80 g, 200 mmol)  
11 was dissolved in 500 mL acetone and 100 mL water was added, followed  
12 by 1.00M NaOH (220 mL, 220 mmol, 110 mol %) over 20 min. The reaction  
13 may be followed by observing disappearance of 13 at 322 nm. After  
14 addition, UV indicated 96% consumption of 13. After 10 more min,  
15 the acetone and some of the water was evaporated, and the aqueous  
16 solution extracted with ether. The product precipitated when 1M  
17 HCl was slowly added to pH 3. After collection by filtration  
18 and drying, product (52 g, 88% yield) was obtained of mp 124-127°.  
19 Recrystallization from ethyl acetate gave pure pyrrole acid 14:  
20 mp 142-144°; TLC (Et<sub>2</sub>O) 0.5; UV (CH<sub>3</sub>OH),  $\lambda_{\max}$  226 nm ( $\epsilon$  13,000); NMR  
21  $\delta$  1.5-2.2 (4H, m), 2.60 (2H, br t), 3.37 (1H, t), 3.72 (6H, s, CO<sub>2</sub>CH<sub>3</sub>),  
22 3.78 (3H, s, NCH<sub>3</sub>), 5.89 (1H, d, J=4.5), 6.98 (1H, d, J=4.5),  
23 8.2 (1H, br, CO<sub>2</sub>H); MS m/e 297 (7, M<sup>+</sup>), 280 (25, M<sup>+</sup>-OH), 94 (100).  
24 Anal. Calcd. for C<sub>14</sub>H<sub>19</sub>NO<sub>6</sub>: C, 56.6; H, 6.4; N, 4.7. Found:  
25 C, 56.5; H, 6.4; N, 4.6.

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

1 suspended in 450 mL methanol and hydrogenated (50 psi) over 5%  
2 Rh/Al<sub>2</sub>O<sub>3</sub> (8.9 g) for 4 days. The reduction was monitored by UV  
3 which indicated that about 15% of the starting material remained  
4 unreduced. The catalyst was removed by filtration and the solvent  
5 evaporated, leaving a white semisolid which was suspended in  
6 water (250 ml), to remove the remaining insoluble starting  
7 material (1.6 g, 18%). After washing with CH<sub>2</sub>Cl<sub>2</sub>, the water was  
8 evaporated, leaving a hygroscopic glass, the hydrate of proline  
9 derivative 15 (6.5 g, 68% crude). This was dissolved in 60 mL  
10 CH<sub>2</sub>Cl<sub>2</sub> in which was passed HCl (g) for 1 min then cooled to 0° for  
11 2 h. Ether was added to flocculate the precipitate which was  
12 filtered, washed with acetone then CH<sub>2</sub>Cl<sub>2</sub> and dried to afford  
13 15 HCl (6.5 g, 64% yield, 78% based on 14 consumed): mp 166-170°d;  
14 TLC (CHCl<sub>3</sub>/CH<sub>3</sub>OH/NH<sub>4</sub>OH, 80/19/1) 0.35; NMR δ 1.2-2.5 (10H, m),  
15 2.91 (3H, s, NCH<sub>3</sub>), 3.0-4.4 (3H, m), 3.73 (6H, s, CO<sub>2</sub>CH<sub>3</sub>); IR 3400,  
16 2940, 1720, 1620 cm<sup>-1</sup>. Anal. Calcd. for C<sub>14</sub>H<sub>24</sub>NO<sub>6</sub>Cl: C, 49.8;  
17 H, 7.2; N, 4.1. Found: C, 49.7; H, 7.2; N, 4.0.

18 5-[4-Bis(methoxycarbonyl)butyl]-3,4-dihydro-1-methyl-2H-  
19 pyrrolium (16) was prepared from amino acid hydrochloride 15  
20 following the procedure used to prepare 31 below. The light brown  
21 crude iminium salt 16 showed IR (POCl<sub>3</sub>) 1750 (s), 1730 (s), 1680 (w)  
22 cm<sup>-1</sup>; NMR (POCl<sub>3</sub>) δ 1.2-3.5 (12H, m), 3.52 (3H, br s, NCH<sub>3</sub>), 3.62  
23 (6H, s, CO<sub>2</sub>CH<sub>3</sub>), 8.48 (1H, br s, N=CH).

24 Methyl 2-Methoxycarbonyl-5-(1-methyl-2-pyrrolidinyl)pentanoate  
25 (17). A. The crude iminium salt 16 (from 100 mg 15, 0.30 mmol) was  
26 cooled to 0° and dissolved in water (2 mL, pH 1.0) then hydrogenated  
27 (40 psi) over 20 mg PtO<sub>2</sub> for 1 hr. After removal of the catalyst

1 and basification to pH 9.8, the product 17 was extracted into  
2  $\text{CH}_2\text{Cl}_2$ : 74 mg, 97% yield.

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

7 C. Pyrrole 12 (270 mg) was hydrogenated in acetic acid (3 mL)  
8 with  $\text{PtO}_2$  (30 mg) and  $\text{H}_2$  (50 psi) for 24 h. The acetic acid was  
9 removed, and the residue subject to an acid-base partition followed  
10 by kugelrohr distillation ( $120^\circ/0.1$  mm) to afford the product  
11 as a clear oil (195 mg, 71% yield). TLC ( $\text{CHCl}_3/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ , 80/19/1)  
12 0.5; GC ( $200^\circ$ ) 1.6 min; NMR  $\delta$  1.1-2.1 (12H, m), 2.26 (3H, s,  $\text{NCH}_3$ ),  
13 3.0 (1H, m), 3.34 (1H, t), 3.70 (6H, s,  $\text{CO}_2\text{CH}_3$ ).

14 Dimethyl 9-Methyl-9-azabicyclo[4.2.1]nonane-2,2-dicarboxylate  
15 (18). The crude iminium salt 16 (from 100 mg of 15, 0.30 mmol) was  
16 cooled to  $0^\circ$  and 0.5 mL water was added with stirring. Saturated  
17  $\text{Na}_2\text{CO}_3$  was rapidly added to pH 9.8 at  $20^\circ$ , and the mixture was  
18 immediately extracted three times with  $\text{CH}_2\text{Cl}_2$ . The organic phase  
19 was dried and the solvent evaporated, leaving crude product (23 mg)  
20 which was kugelrohr distilled ( $100-120^\circ/0.1$  mm) to afford bicyclo  
21 malonate 18 as a clear oil (18 mg, 24%): TLC ( $\text{CHCl}_3/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ ,  
22 80/19/1) 0.75; GC ( $200^\circ$ ) 1.45 min. NMR  $\delta$  1.2-2.5 (10H, m), 2.49  
23 (3H, s,  $\text{NCH}_3$ ), 3.1 (1H, m), 3.65 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 3.68 (3H, s,  
24  $\text{CO}_2\text{CH}_3$ ), 3.8 (1H, m); MS  $m/e$  255 (10,  $\text{M}^+$ ), 224 (10,  $\text{M}^+-\text{OCH}_3$ ), 96 (50),  
25 82 (100). Anal. Calcd. for  $\text{C}_{13}\text{H}_{21}\text{NO}_4$ : C, 61.2; H, 8.3; N, 5.5.  
26 Found: C, 61.4; H, 8.3; N, 5.3.

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

1 The bicyclic malonate (18, 98 mg) was dissolved in 6M HCl (2 ml)  
2 and rapidly heated to reflux under nitrogen. The HCl was evaporated  
3 after 7.5 h, affording the acid as a clear glass. This was  
4 esterified by refluxing in CH<sub>3</sub>OH with catalytic sulfuric acid for  
5 17h beneath a soxhlet extractor filled with 3A molecular sieves.  
6 Evaporation of most of the solvent, basification with Na<sub>2</sub>CO<sub>3</sub>, and  
7 extraction into CH<sub>2</sub>Cl<sub>2</sub> followed by kugelrohr distillation (70-90°/  
8 1.4 mm) afforded the bicyclo monoester 21a: 40.1 mg, 53%; GC (200°)  
9 0.65 min. NMR δ 1.2-2.5 (11H, m), 2.40 (3H, s, NCH<sub>3</sub>), 3.1-3.5  
10 (2H, m), 3.65 (3H, s, CO<sub>2</sub>CH<sub>3</sub>); MS m/e 197 (18, M<sup>+</sup>), 82 (100);  
11 Anal. Calcd for C<sub>11</sub>H<sub>19</sub>NO<sub>2</sub>: C, 67.0; H, 9.7; N, 7.1. Found:  
12 C, 66.6; H, 9.6; N, 7.0.

fn 22

13 4-Methoxycarbonylbutanoyl Chloride (22) was prepared by  
14 a modification of the previous procedure.<sup>22</sup> Glutaric anhydride  
15 (62.8 g, 550 mmol) and anhydrous methanol (17.6 g, 550 mmol) were  
16 heated at 100° for 1.5 hr. The monomethyl ester was cooled and  
17 SOCl<sub>2</sub> (50 ml, 685 mmol, 125 mol %) was added, resulting in an endo-  
18 thermic reaction and gas evolution. The temperature was slowly  
19 raised to 70° for 1 hr. After cooling, excess SOCl<sub>2</sub> was evaporated  
20 and the acid chloride distilled at 100°/14 mm: 71 g, 79% yield;  
21 NMR δ 1.8-2.6 (4H, m), 2.99 (2H, t), 3.67 (3H, s).

22 Methyl 4-(1-Methyl-2-pyrrolylcarbonyl)pentanoate (23). The  
23 acid chloride of hydrogen methyl glutarate (22) (26.2 g, 154 mmol)  
24 was dissolved in 100 ml CH<sub>2</sub>Cl<sub>2</sub> and mixed with aluminum chloride  
25 (22 g, 165 mmol, 107 mol %). This mixture was added to a stirred  
26 solution of 1-methylpyrrole (15 g, 185 mmol, 120 mol %) in 100 ml  
27 CH<sub>2</sub>Cl<sub>2</sub> at -40°, maintaining about i.t. -20°. After 15 min, 1.5 g

1 more 1-methylpyrrole was added and stirring continued 45 min at  
2 i.t. -25° and 1 hr at +20°. The solvent was removed, and 200 ml  
3 ice and water added to the cooled mixture, which was extracted  
4 into ether (4 x) and the ether layer washed with saturated sodium  
5 carbonate solution, saturated NaCl, and dried. The crude product  
6 (27.2 g) was a mixture of 2- and 3-isomers, 23 and 24: TLC (Et<sub>2</sub>O) 23,  
7 0.6; 24, 0.4; GC (210°) 23, 1.1; 24, 2.2 min. The 2-isomer, 23, was  
8 distilled through a vacuum-jacketed column fitted with a platinum  
9 screen (bp 120°, 0.4 mm): mp 37-39°; yield 16.5 g, 51%; NMR δ  
10 2.2 (4H, m), 2.79 (2H, t), 3.61 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 3.88 (3H, s, NCH<sub>3</sub>),  
11 6.01 (1H, dd), 6.68 (1H, m), 6.86 (1H, dd). Anal. Calcd for  
12 C<sub>11</sub>H<sub>15</sub>NO<sub>3</sub>: C, 63.1; H, 7.2; N, 6.7. Found: C, 63.2; H, 7.2;  
13 N, 6.7.

14 Methyl 4-(1-Methyl-3-pyrrolylcarbonyl)pentanoate (24) was  
15 the major component of the higher boiling fraction, 7.1 g (22%),  
16 bp 165°/0.1 mm. A sample was purified by chromatography on silica  
17 gel, eluting with ether: NMR δ 2.2 (4H, m), 2.72 (2H, t), 3.61  
18 (6H, s, NCH<sub>3</sub>CO<sub>2</sub>CH<sub>3</sub>), 6.48 (2H, d, J=2Hz), 7.17 (1H, m).

19 5-(1-Methyl-2-pyrrolyl)pentanoic Acid (25). As in a similar  
fn 23 20 case, <sup>23</sup> the ketone (23, 20.7 g, 99 mmol) was stirred with dry  
21 ethylene glycol (180 ml) and hydrazine hydrate (85% in water, 17 ml,  
22 14.5 g, 290 mmol, 290 mol %) at 100° for 15 min. Potassium hydroxide  
23 (24 g, 430 mmol, 430 mol %) was added slowly and the bath temperature  
24 raised slowly (1.5 hr) to 210°, removing the water and excess  
25 hydrazine by distillation. Heating at i.t. 190° was continued  
26 4.5 hr, the solution was cooled, acidified to pH 2.0, extracted with  
27 ether (5 x), dried, and the ether evaporated to afford essentially

1 pure acid 25 as a light yellow solid, mp 58-61°, 17.9 g (100% yield).  
2 Kugelrohr distillation (110°/0.2 mm) afforded white crystals,  
3 mp 71-73°: NMR  $\delta$  1.7 (4H, m), 2.4 (4H, m), 3.46 (3H, s, NCH<sub>3</sub>),  
4 5.80 (1H, t), 6.41 (1H, t). Anal. Calcd for C<sub>10</sub>H<sub>15</sub>NO<sub>2</sub>: C, 66.3;  
5 H, 8.3; N, 7.7. Found: C, 66.2; H, 8.2; N, 7.7.

6 6-(1-Methyl-2-pyrrolyl)-2-hexanone (26). The carboxylic acid  
7 (25, 17.9 g, 99 mmol) was converted to its lithium salt with lithium  
8 hydroxide monohydrate (4.22 g, 101 mmol, 102 mol %) in 40 mL hot  
9 water; 10 min after homogeneity was achieved, the water was  
10 evaporated and the product further dried in a vacuum dessicator  
11 for 24 hr, yielding the lithium salt of 25 (17.9 g, 97% yield).

12 The lithium salt and triphenylmethane (18 mg) were suspended  
13 in 180 mL THF and methyl lithium (49 ml of 2.1M, 103 mmol, 104 mol %)   
14 was added over 0.5 hr until all the starting material dissolved  
15 and a persistent orange-red color appeared. After stirring 9 hr,  
16 the reaction mix was cooled to 0° and added to a stirred mixture of  
17 HCl (15 ml of 12M, 180 mmol, 180 mol %), water and ice (200 ml).  
18 The layers were separated, and the aqueous layer, after basification,  
19 was extracted 3 x with ether. The combined organic layers were  
20 dried, the solvent evaporated, and the crude product (15.7 g, 87%)  
21 was kugelrohr distilled (105°/1.5 mm) to afford ketone 26: 13.3 g,  
22 75% yield; TLC (Et<sub>2</sub>O) 0.65; GC (210°) 0.65 min; NMR  $\delta$  1.65 (4H, s),  
23 2.11 (3H, s, COCH<sub>3</sub>), 2.5 (4H, m), 3.50 (3H, s, NCH<sub>3</sub>), 5.86  
24 (1H, m), 6.01 (1H, t), 6.51 (1H, t). Anal. Calcd for C<sub>11</sub>H<sub>17</sub>NO:  
25 C, 73.7; H, 9.6; N, 7.8. Found: C, 74.0; H, 9.6; N, 7.7.

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



1 ether (87 ml) and trichloroacetyl chloride (6.0 ml, 54 mmol, 110 mol %)   
2 was added. After 1 hr the solvent was removed to afford 27 as a red   
3 oil, 16.5 g, 105% yield. Including 200 mol % anhydrous  $K_2CO_3$  in   
4 the reaction resulted in a lower (71%) yield of slightly purer   
5 material: TLC ( $Et_2O$ ) 0.60; NMR  $\delta$  1.7 (4H, m), 2.16 (3H, s,  $COCH_3$ ),   
6 2.55 (4H, m), 3.87 (3H, s,  $NCH_3$ ), 6.05 (1H, d), 7.47 (1H, d).

7 6-(5-Methoxycarbonyl-1-methyl-2-pyrrolyl)-2-hexanone (28).

8 The crude trichloroacetyl pyrrole 27 was dissolved in 30 ml   
9 methanol and a solution of sodium methoxide prepared from sodium   
10 (450 mg, 19.5 mmol, 40 mol %) and 50 mL methanol was added over   
11 5 min. The red color faded to amber and  $\lambda_{max}$  shifted from 322 to   
12 272 nm. After stirring 0.5 hr, the methanol was evaporated and   
13 ether (100 ml) and water (50 ml) were added. The organic layer   
14 was washed with saturated NaCl, dried and the ether evaporated to   
15 afford 10.4 g crude product. Kugelrohr distillation (130°/0.25 mm)   
16 afforded the ketoester 28: 8.04 g, 70% yield from 26; mp 32-33°;   
17 TLC ( $Et_2O$ ) 0.6; GC (260°) 0.65 min; NMR  $\delta$  1.7 (4H, m), 2.12 (3H,   
18 s,  $COCH_3$ ), 2.5 (4H, m), 3.76 (3H, s,  $CO_2CH_3$ ), 3.81 (3H, s,  $NCH_3$ ),   
19 5.88 (1H, d), 6.84 (1H, d). Anal. Calcd for  $C_{13}H_{19}NO_3$ : C, 65.8;   
20 H, 8.1; N, 5.9. Found: C, 66.0; H, 8.2; N, 5.9.

21 6-(5-Methoxycarbonyl-1-methyl-2-pyrrolidinyl)-2-hexanol (29).

22 The pyrrole ketoester (28, 7.84 g, 33.2 mmol) was dissolved in 50 mL   
23 methanol and a solution of sulfuric acid (5.6 ml, 100 mmol, 3.00 mol   
24 %) in 50 mL methanol was added. The solution was hydrogenated   
25 (40-50 psi) over 5% rhodium on alumina (7.84 g) for 44 hr, monitoring   
26 the progress of the reduction by UV. After removing the catalyst,   
27 the solvent was evaporated, water was added, the pH was adjusted to

1 1.5-2.0, and the aqueous solution was extracted 2 x with ether.  
2 The aqueous phase was then adjusted to pH 9.8 with saturated  
3  $\text{Na}_2\text{CO}_3$  and extracted 4 x with  $\text{CH}_2\text{Cl}_2$ . After drying and evaporation  
4 of the solvent, the crude product (7.5 g) was kugelrohr distilled  
5 (110°/0.15 mm) to afford pyrrolidine 29 as a clear oil (6.3 g,  
6 78% yield): TLC ( $\text{CHCl}_3/\text{CH}_3\text{OH}/\text{NH}_4$ , 90/9.5/0.5) 0.5; GC (200°)  
7 1.7 min; NMR  $\delta$  1.16 (3H, d,  $\text{HOCCH}_3$ ), 1.1-2.3 (15H, m), 2.30 (3H,  
8 s,  $\text{NCH}_3$ ), 2.96 (1H, br t), 3.69 (3H, s,  $\text{CO}_2\text{CH}_3$ ). Anal. Calcd for  
9  $\text{C}_{13}\text{H}_{25}\text{NO}_3$ : C, 64.2; H, 10.4; N, 5.8. Found: C, 64.1; H, 10.2;  
10 N, 5.7.

11 6-(5-Methoxycarbonyl-1-methyl-2-pyrrolidinyl)-2-hexanonate (30a).

12 Jones reagent was prepared from  $\text{CrO}_3$  (2.67 g, 26.7 mmol), sulfuric  
13 acid (2.3 ml, 41.5 mmol) and water (to 10.0 ml). Alcohol 29 (2.64 g,  
14 10.9 mmol) was dissolved in 15 mL acetone and Jones reagent (4.0 ml,  
15 10.7 mmol, 98 mol %) was added with mixing over 5 min and the  
16 exothermic reaction mixture was shaken for 5 min. Saturated  
17 aqueous sodium bicarbonate (40 ml) was added, the lower aqueous  
18 layer removed, and the upper acetone layer extracted once with  
19  $\text{CH}_2\text{Cl}_2$ . The combined aqueous layers were extracted 4 x with  $\text{CH}_2\text{Cl}_2$ ,  
20 the organic extract was dried and evaporated and the product  
21 purified by kugelrohr distillation (90-100°/0.15 mm): yield,  
22 2.30 g, 88%; TLC ( $\text{CHCl}_3/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ , 90/9.5/0.5) 0.7; GC (200°)  
23 1.7 min, coinjects with 29; NMR  $\delta$  1.1-2.6 (13H, m), 2.11 (3H, s,  
24  $\text{COCH}_3$ ), 2.32 (3H, s,  $\text{CO}_2\text{CH}_3$ ), 2.97 (1H, br t), 3.71 (3H, s,  $\text{CO}_2\text{CH}_3$ ).  
25 Anal. Calcd for  $\text{C}_{13}\text{H}_{23}\text{NO}_3$ : C, 64.7; H, 9.6; N, 5.8. Found:  
26 C, 64.7; H, 9.6; N, 5.8.  
27

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<sub>4</sub> and KOH: yield, 2.18 g, 103%; mp 130-133°C; TLC (CHCl<sub>3</sub>/CH<sub>3</sub>OH/NH<sub>4</sub>OH, 80/19/1) 0.2-0.4; IR (nujol) 3350 (w), 2900, 1725, 1700 cm<sup>-1</sup>; NMR δ 1.2-2.8 (12H, m), 2.18 (3H, s, COCH<sub>3</sub>), 2.94 (3H, s, NCH<sub>3</sub>), 3.3 (1H, m), 4.22 (1H, br t). Anal. Calcd for C<sub>12</sub>H<sub>22</sub>NO<sub>3</sub>Cl: 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<sub>3</sub> (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<sub>3</sub> was rapidly removed with a stream of nitrogen, leaving the crude iminium salt 31: IR (POCl<sub>3</sub>), 2930, 1710 (s), 1680 (w) cm<sup>-1</sup>; NMR δ 1.3-3.5 (11H, m), 2.05 (3H, s, COCH<sub>3</sub>), 3.56 (3H, br s, NCH<sub>3</sub>), 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<sub>2</sub> (15 mg). Basification and extraction into CH<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub> (20 mg).

1 Partition between aq. alkali and  $\text{CH}_2\text{Cl}_2$  afforded 32: yield,  
2 85 mg, 75%; GC (200°) 0.65 min; NMR  $\delta$  1.18 (3H, d), 1.2-2.3  
3 (16H, m), 2.29 (3H, s,  $\text{NCH}_3$ ), 2.86 (1H, s, OH), 3.0 (2H, m), 3.67  
4 (1H, t).

5 6-(1-Methyl-2-pyrrolidinyl)-2-hexanone (33). A. Iminium  
6 salt 31, hydrogenated as above, but at pH 1.5, afforded 33.

7 B. Jones oxidation of 32 following the procedure used to  
8 prepare 30a afforded 33 in 90% yield: GC (200°) 0.65 min;  
9 NMR  $\delta$  1.2-2.6 (13H, m), 2.12 (3H, s,  $\text{COCH}_3$ ), 2.29 (3H, s,  $\text{NCH}_3$ ),  
10 3.0 (2H, m).

11 2-Acetyl-9-methyl-9-azabicyclo[4.2.1]nonane (34). A. The  
12 crude iminium salt 31 (5.40 mmol) was cooled to room temperature,  
13 dissolved in 30 mL methanol and heated to reflux for 16 hr. The  
14 mixture then was cooled, the methanol evaporated and replaced with  
15 water, the acidic aqueous solution was extracted twice with ether  
16 to remove trimethyl phosphate, then basified to pH 10 with sat.  
17 sodium carbonate and extracted 4 x with  $\text{CH}_2\text{Cl}_2$ . After drying and  
18 evaporation of solvent, the crude product (1.07 g) obtained was  
19 purified by kugelrohr distillation (60-65°/0.5 mm) to afford 34 as  
20 a clear oil: yield, 470 mg, 49%; TLC ( $\text{CHCl}_3/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ , 80/19/1)  
21 0.55 (variable, tailing); GC (200°) 0.75 min; IR 3400, 2920, 1705  
22  $\text{cm}^{-1}$ ; (lit.<sup>5</sup> 1705  $\text{cm}^{-1}$ ); NMR  $\delta$  1.3-2.5 (11H, m), 2.12 (3H, s,  $\text{COCH}_3$ ),  
23 2.39 (3H, s,  $\text{NCH}_3$ ), 3.3 (2H, m) [lit.<sup>5</sup> 2.09, 2.12 (singlets, ratio  
24 1:2), 2.38, 2.48 (singlets, ratio 1:2)]; MS m/e 181 ( $\text{M}^+$ , 32), 138  
25 ( $\text{M}^+ - \text{COCH}_3$ , 30), 82 (100). Anal. Calcd. for  $\text{C}_{11}\text{H}_{19}\text{NO}$ : C, 72.9;  
26 H, 10.6; N, 7.7. Found: C, 72.7; H, 10.5; N, 7.6.

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

1 with no decomposition. Contrary to a previous observation<sup>5</sup>  
2 NMR revealed only one epimer, and no epimerization was observed  
3 after 3 hr at pH 10. The hydrochloride of 34 was an extremely  
4 hygroscopic white powder; mp 121-125°C (lit.<sup>5</sup> mp 152-155°);  
5 single enantiomer, NMR  $\delta$  2.22 (3H, s, COCH<sub>3</sub>), 2.90 (3H, s,  
6 NCH<sub>3</sub>) [lit.  $\delta$  2.22 (3H, s), 2.91 (3H, s)]; LD<sub>50</sub> > 25 mg/kg (ip, mouse).

7 B. Ester 21a (6.6 mg, 0.0335 mmol) was hydrolyzed in 0.1M  
8 aqueous LiOH (105 mol %) for 1 h, then dried (60°/1 mm/18 h) and  
9 pulverized affording lithium salt 21b. This was suspended in DME  
10 (0.5 ml) and treated with CH<sub>3</sub>Li using the procedure employed to  
11 prepare 26. The product was purified by kugelrohr distillation  
12 (3.4 mg, 56% yield) and was identical with 34 prepared above.

13 2-Acetyl-9-(2,2,2-trichloroethoxycarbonyl)-9-azabicyclo[4.2.1]-  
14 nonane (35a). Bicyclic ketone 34 (100 mg, 0.55 mmol) was dissolved  
15 in anhydrous benzene (1 mL), 2,2,2-trichloroethoxycarbonyl chloride  
16 (0.10 mL, 0.726 mmol, 130 mol %) was added, and the solution was  
17 refluxed for 20 hr. The benzene was evaporated and replaced with  
18 ether and the ethereal solution was applied to silica gel (200 mg),  
19 eluting with ethyl acetate. Excess 2,2,2-trichloroethoxycarbonyl  
20 chloride was evaporated, leaving reasonably pure 35a as a yellow oil  
21 (153 mg, 81% yield): TLC (Et<sub>2</sub>O/EtOAc, 99/1) 0.6 (minor), 0.65  
22 (major); GC (270°) 1.1 (80%), 1.25 (15%), 1.8 (5%) min; NMR  $\delta$   
23 1.2-2.5 (11H, m), 2.15 (3H, s, COCH<sub>3</sub>), 4.2-4.8 (2H, m), 4.78 (2H,  
24 s, CH<sub>2</sub>CCl<sub>3</sub>) and 2.79 (s, NCH<sub>3</sub> in side product).

25 2-Acetyl-9-azabicyclo[4.2.1]nonane (35b). The trichloro-  
26 ethyl carbamate (35a, 69 mg, 0.20 mmol) was dissolved in glacial  
27 acetic acid/water, 9/1 (0.7 ml) and zinc dust (100 mg, 1.5 mmol,

1 750 mol %) was added portionwise. After 2.5 h, the zinc was removed  
2 and the solvent evaporated, leaving a residue which was dissolved in  
3  $\text{CH}_2\text{Cl}_2$  and shaken with saturated sodium carbonate. The product was  
4 rapidly extracted from the  $\text{CH}_2\text{Cl}_2$  layer with 0.1M HCl, and the  
5 aqueous acid evaporated to afford the hydrochloride salt of 35b  
6 as a light orange oil (29 mg, 71% yield): TLC ( $\text{CHCl}_3/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ ,  
7 80/19/1), 0.3-0.4; NMR  $\delta$  1.5-3.3 (11H, m), 2.23 (3H, s,  $\text{COCH}_3$ ),  
8 4.2 (2H, m);  $\text{LD}_{50} = 2.5 \text{ mg/kg}$  (ip, mouse).

9  
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References and Notes

- (1) W. W. Carmichael, D. F. Biggs, and P. R. Gorham, Science, 187, 542 (1975).
- (2) C. S. Huber, Acta. Cryst. B, 78, 2577 (1972).
- (3) J. P. Devlin, O. E. Edwards, P. R. Gorham, N. R. Hunter, R. K. Pike, and B. Stavric, Can. J. Chem., 55, 1367 (1977)
- (4) A. C. Cope, H. R. Nace, and L. L. Estes, J. Am. Chem. Soc., 72, 1123 (1950).
- (5) H. F. Campbell, O. E. Edwards, and R. Kolt, Can. J. Chem., 55, 1372 (1977).
- (6) W. Parker, R. A. Raphael, and D. I. Wilkinson, J. Chem. Soc., 2433 (1959).
- (7) P. Karrer and H. Alagil, Helv. Chim. Acta., 30, 1776 (1947).
- (8) M. E. Kuehne, Synthesis, 510, (1970)
- (9) E. Wenkert, K. G. Dave, and R. V. Stevens, J. Am. Chem. Soc., 90, 6177 (1968); R. V. Stevens, Acc. Chem. Res., 10, 193 (1977).
- (10) R. T. Dean, H. C. Padgett, and H. Rapoport, J. Am. Chem. Soc., 98, 7448 (1976).
- (11) J. I. Crowley and H. Rapoport, J. Am. Chem. Soc., 92, 6363 (1970).
- (12) S. F. Findlay, J. Org. Chem., 22, 1385 (1957); R. Robinson, J. Chem. Soc. 111, 762 (1917).
- (13) J. Harbuck and H. Rapoport, J. Org. Chem., 37, 3618 (1972).
- (14) F. Bohlmann, H.-J. Muller, and D. Schumann, Chem. Ber., 106, 3026 (1973).
- (15) N. J. Leonard and A. G. Cook, J. Am. Chem. Soc., 81, 5627 (1959).
- (16) A. Buzas, R. Cavier, F. Cossais, J. Finet, J. Jacquet, G. Lavielle, and N. Platzler, Helv. Chim. Acta, 60, 2122 (1977)
- (17) C. F. Candy, R. A. Jones, and P. H. Wright, J. Chem. Soc. C, 2563, (1970).

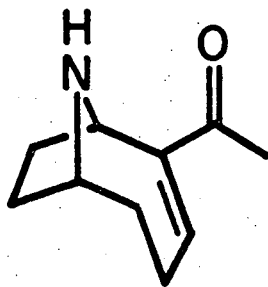
- (18) R. E. Strube, "Organic Synthesis", Coll. Vol. 4, Wiley, N.Y., 1963, p. 417
- (19) W. Kutscher and ). Klammerth, Hoppe-Seylers Z. Physiol. Chem. 289, 232 (1952).
- (20) M. Regitz, J. Hocker and A. Liedhegener, "Organic Synthesis" Coll. Vol. 5, Wiley, N.Y. 1973, p.179.
- (21) R. Silverstein, E. Ryskiewicz, C. Willard, and R. Koehler, J. Org. Chem., 20, 668 (1955); "Organic Synthesis", Coll. Vol. 4, Wiley, N.Y., 1963, p.831.
- (22) W. E. Bachmann, S. Kushner, and A. C. Stevenson, J. Am. Chem. Soc., 64, 977 (1942).
- (23) M. Julia and Y. R. Pascal, Chimie Therapeutique, 274 (1970)



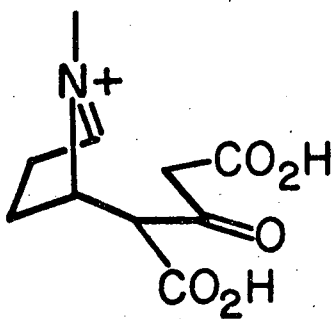
Table I. Effect of pH on Stability of Iminium Salt 16 and Its Cyclization to Bicyclic Malonate 18 at 20°C.

<u>pH</u>	<u>Yield 16</u>	<u>Unreacted 18<sup>a</sup></u>
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%

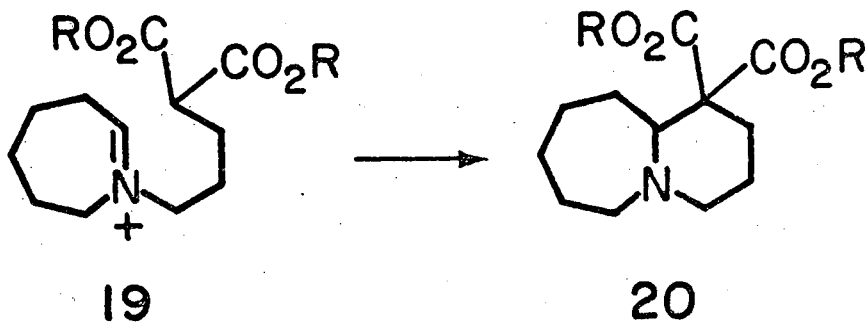
<sup>a</sup>Quantity of 16 and 18 determined after 5 min of reaction. The amount of 16 was determined by reduction to 17.

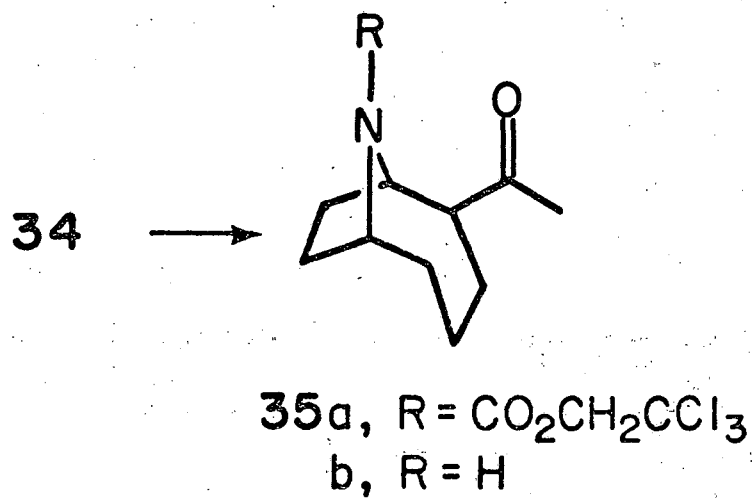
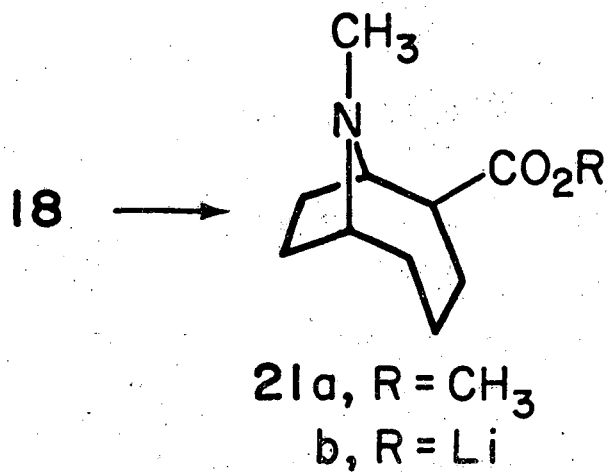


I, Anatoxin-a

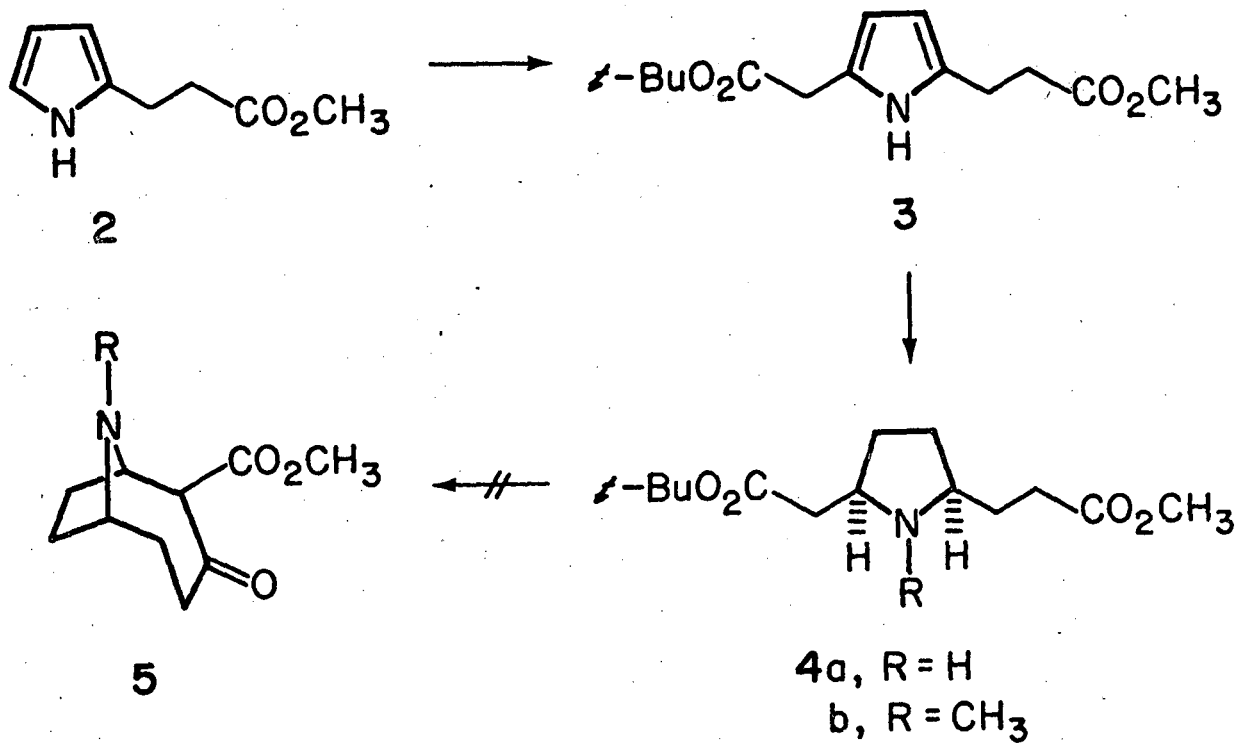


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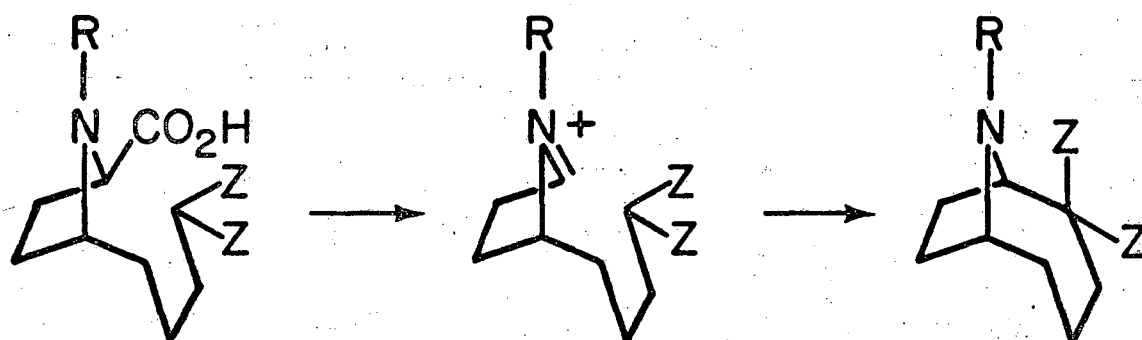




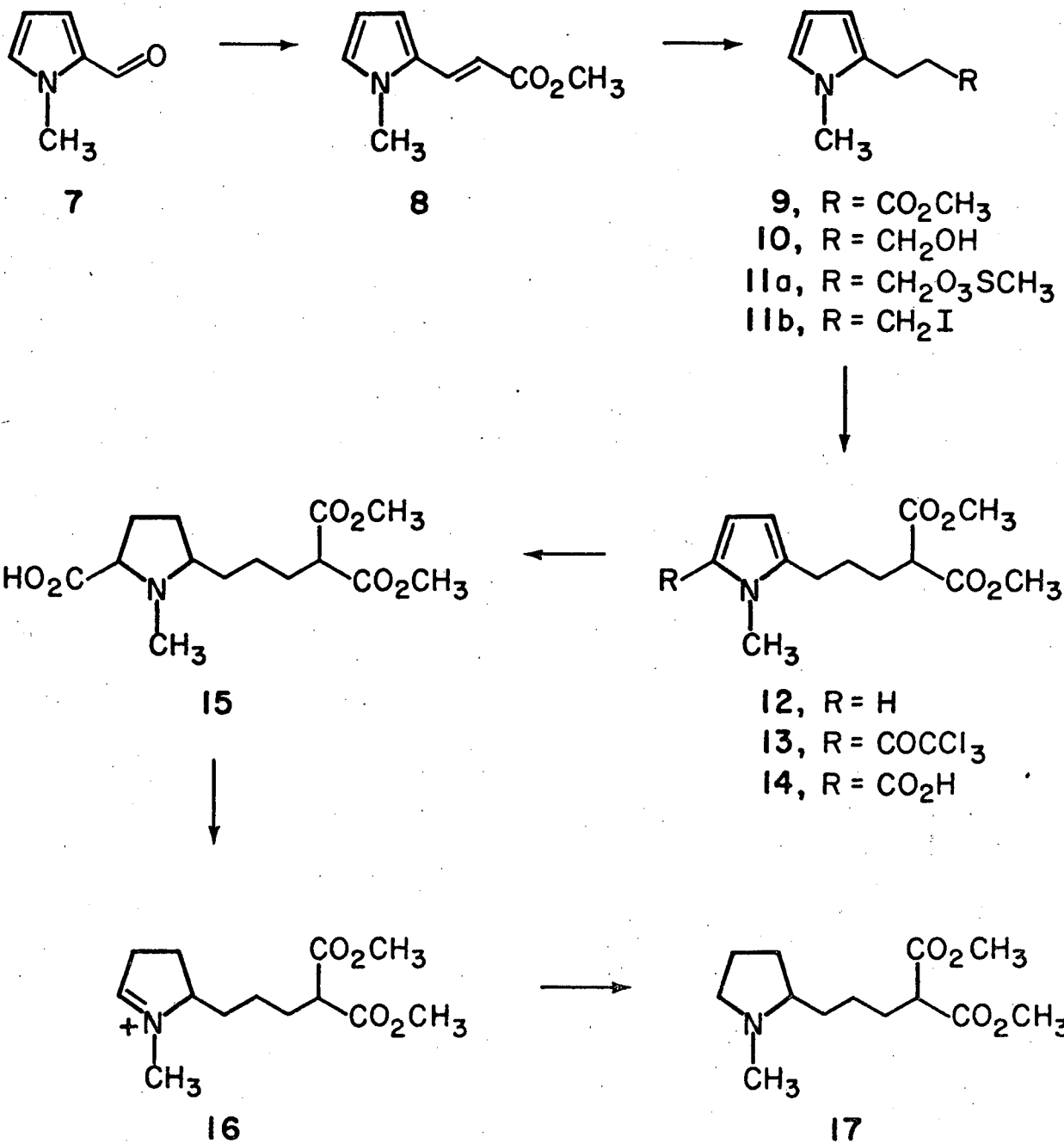
## Scheme I



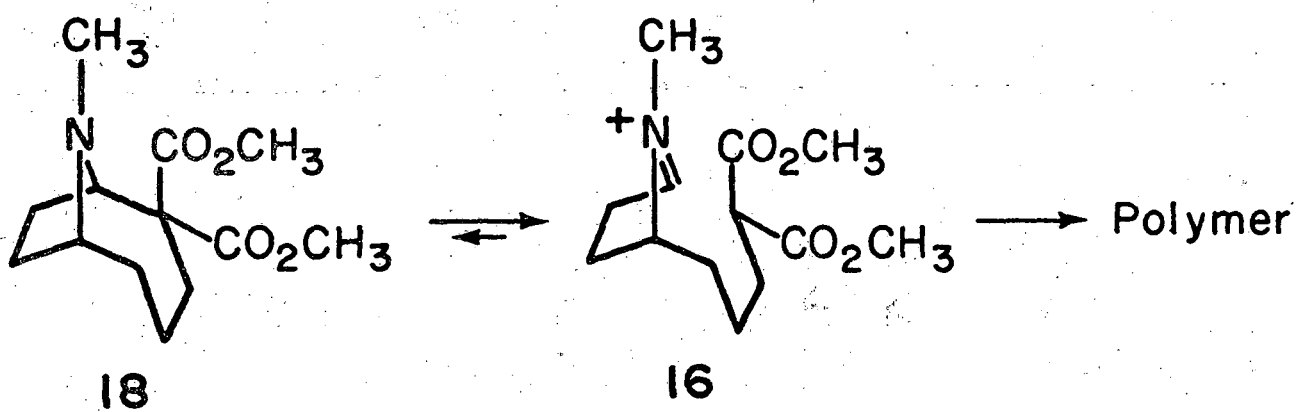
## Scheme II



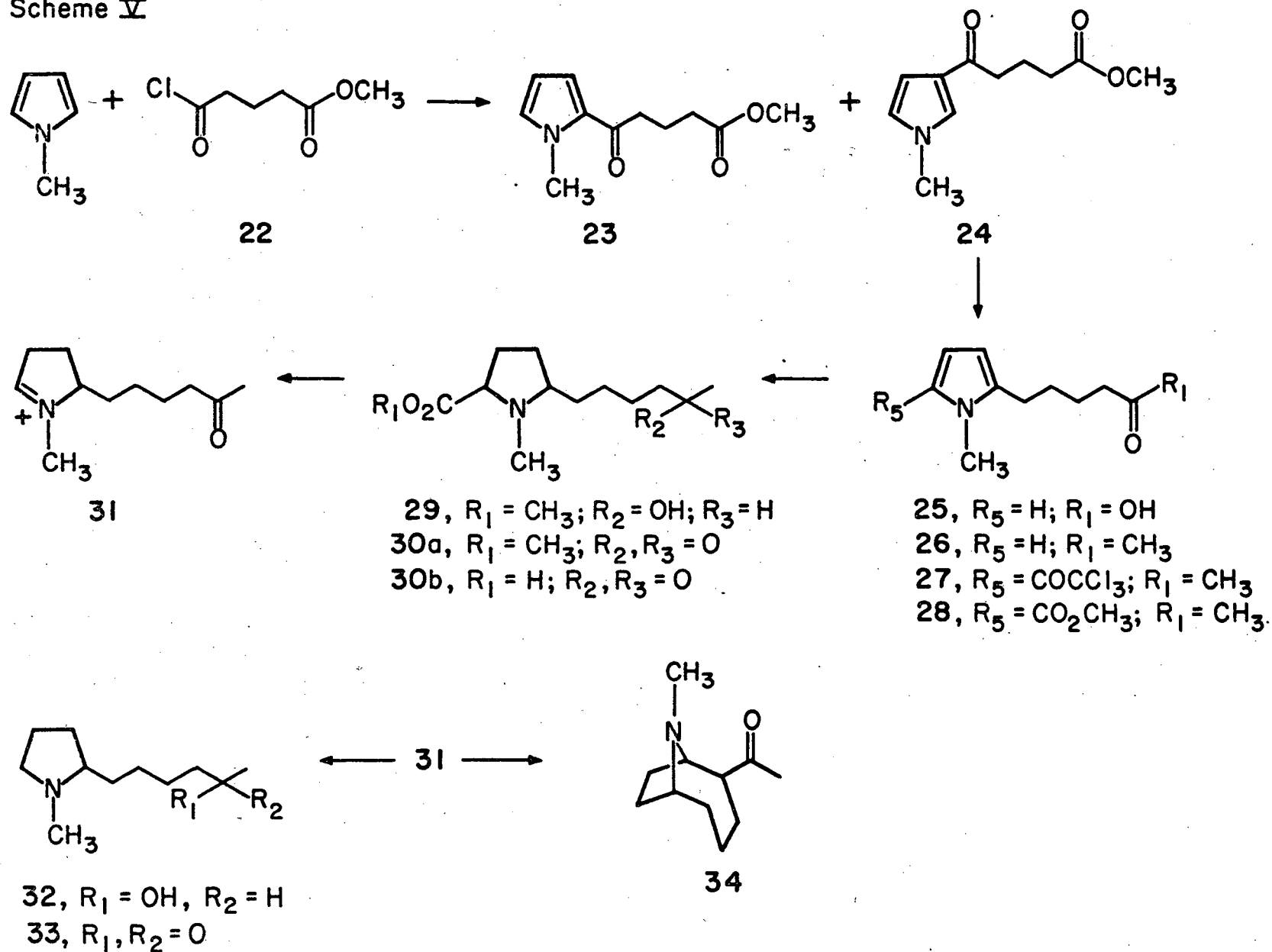
## Scheme III



## Scheme IV



Scheme V





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