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(36) In this treatment we neglect the electrolyte effect of HCl on the cmc.
(37) There is the possibility that the solute strongly perturbs micellar structure. However, Beer's law is obeyed for solutions of 1-nitronaphthalene over a 32-fold change in concentration in solutions of micellized 0.04 M **3a** and 0.02 M **3b**, suggesting that changes in total concentration of the solute did not affect its partitioning between water and the micelles, and therefore did not affect micellar structure.
(38) Even if β is in the low range of ca. 0.6 for a hydroxide ion surfactant, saturation of the Stern layer by OH^- would only increase the concentration of micellar-bound OH^- by ca. 66%, which would not account for the observed rate effects. It would give a micelle of zero net charge which would be unexpected with a hydrophilic counterion.
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Synthesis of Anatoxin *a* via Intramolecular Cyclization of Iminium Salts

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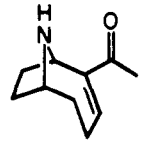
Abstract: Anatoxin *a* (**1**) has been synthesized by exploiting intramolecular cyclization between an iminium salt and a nucleophilic carbon to construct the 9-azabicyclo[4.2.1]nonane ring system. Cyclization of malonate iminium salt **16** at alkaline pH afforded a low yield of bicyclic malonate **18** owing to an unfavorable equilibrium constant and lability of the iminium salt in base. In contrast, cyclization of ketoiminium 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



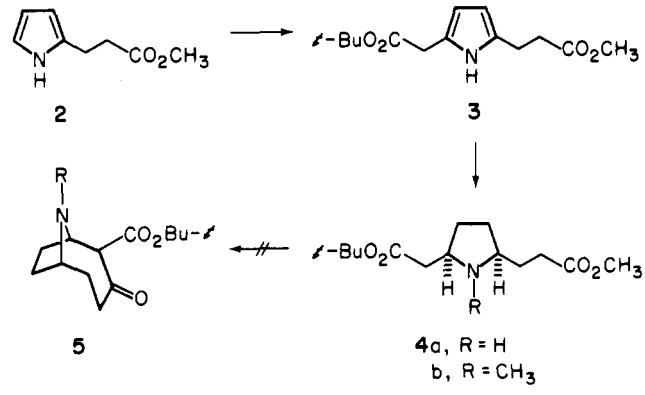
1, Anatoxin-a

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.

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 synthesis 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 paper 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 five- and six-membered rings, and occasionally

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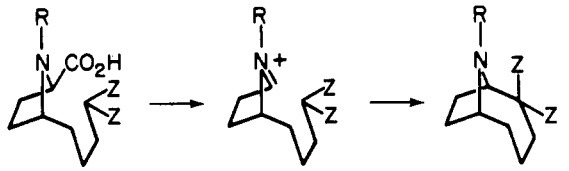
Scheme II

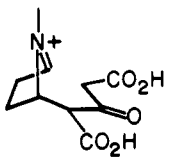


bridged systems,[8,9] and the facility with which these cyclizations occur encouraged us to pursue this approach toward the more challenging strained and bridged 9-azabicyclo[4.2.1]-nonane skeleton of anatoxin *a*. The major encumbrance to synthetic utilization of iminium salts, the absence of a versatile 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.

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 *tert*-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 *tert*-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 *tert*-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 owing 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 methylamine,[12] in which iminium salt intermediate **6** has been proposed, suggested an iminium salt approach to

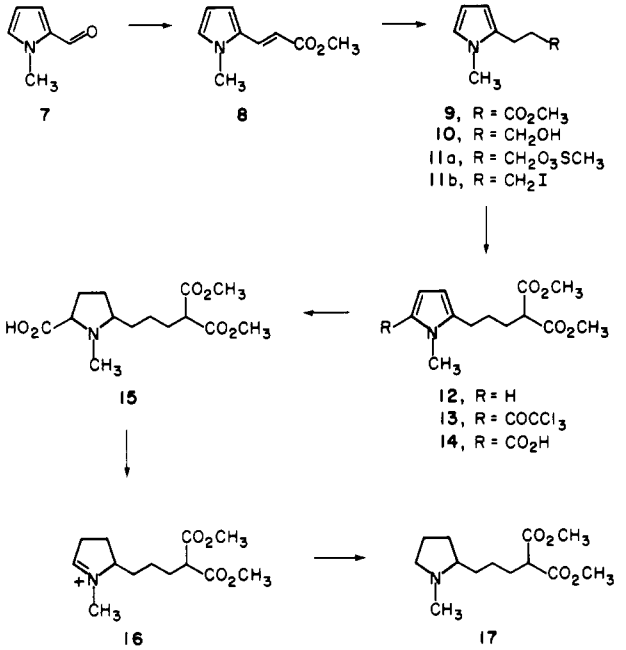


6

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, owing to sensitivity of the electron-rich

Scheme III



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 wth 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 100 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 °C[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 min of reaction between pH 3.0 and 8.8 at 20 °C. 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]

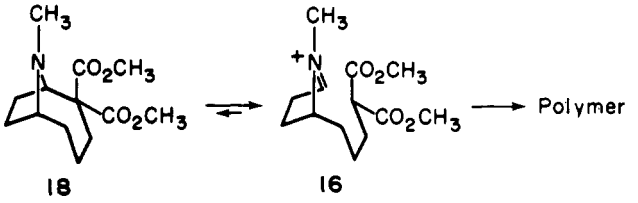
Longer reaction times and higher temperatures did not increase the yield of **18**, but, unexpectedly, had just the opposite effect. This observation suggested that the cyclization was reversible. Indeed, when the isolated bicyclic malonate **18** was placed in water at pH 7 or 10, it decomposed with a half-life

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

pH	yield of **18**, %	unreacted **16**,[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

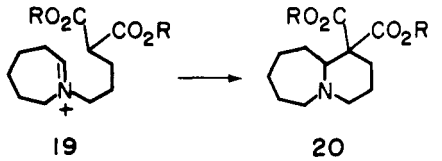
[a] Quantity of **16** and **18** determined after 5 min of reaction. The amount of **16** was determined by reduction to **17**.

Scheme IV



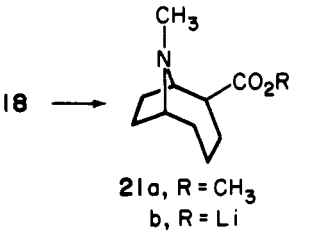
of 10 and 5 min, respectively. Furthermore, in aqueous acid (pH 1-3) **18** formed iminium salt **16** in nearly quantitative yield with a half-life of 2 h. In summary, as shown in Scheme IV, the low yield of **18** is due to an equilibrium very unfavorable toward its formation as well as irreversible 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 20–25% 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 ketoiminium salt **31.**

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 6 M HCl, then reesterified to afford bicyclic ester **21a.** The ester **21a** was hydrolyzed to lithium salt **21b** with LiOH and subsequently treated with methyllithium, 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 °C. Thus we proceeded to prepare ketoiminium salt **31,** confident that it would cyclize to bicyclic ketone **34.**

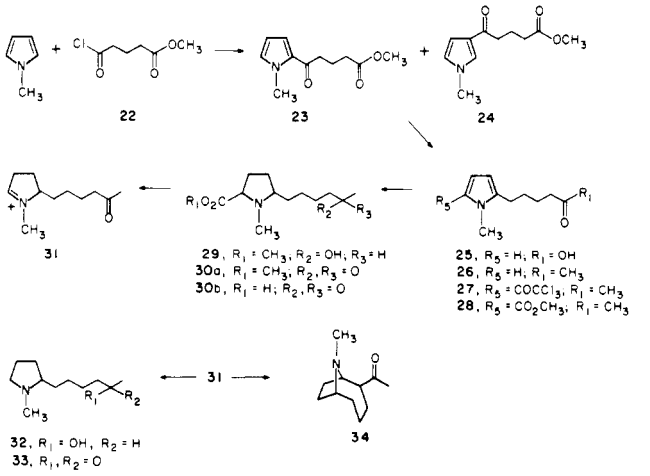


Although ketoiminium salt **31** might have been prepared via nucleophilic displacement from iodide **11b,** we employed a more direct approach for elaborating the ketone side chain, as shown in Scheme V. Friedel-Crafts acylation of 1-methylpyrrole with the acid chloride of hydrogen methyl glutarate (**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 h at 20 °C in water at pH 0.5. After some experimentation, a respectable 47% yield was attained by refluxing **31** in acidic methanol for 14 h. 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 nonreversible polymerization of the iminium salt occur in analogy to Scheme IV.

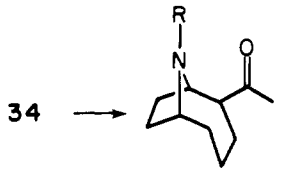
Scheme V



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 completes 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**).



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

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-ft 5% SE-30 column at 40 psi He. Precoated 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 $Ce(SO_4)_2 \cdot 2H_2O$ (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 $CDCl_3$ (Me_4Si 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 2.1 L) was added to methanolic dimethyl malonate (423 g, 3.2 mol, in 2.1 L) over 1 h. After 18 h, the potassium salt (375 g, 2.4 mol) was precipitated by cooling (−13 °C) 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 concentrated HCl (2.4 mmol) at i.t. 5–10 °C and the product was extracted from the aqueous solution and the KCl precipitate 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 °C for 42 h and 70–80 °C for 28 h. Ether (1.8 L) was added and the pyridine and piperidine were extracted into 1.8 M HCl (2 × 2 L). The organic phase was washed with aqueous Na_2CO_3 and 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 °C, 0.3 mm) afforded the product **2** as a clear liquid (58.5 g, 45% yield): mp 8–11 °C (lit.[19] bp 75 °C (0.3 mm)); NMR δ 2.70 (4 H, m), 3.64 (3 H, s), 5.74 (1 H, m), 5.89 (1 H, m), 6.46 (1 H, m).

Methyl 3-(5-*tert*-Butoxycarbonylmethyl-2-pyrrolyl)propanoate (3). *tert*-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 °C. After 1 h more, the solvent was evaporated, starting material (5.2 g) removed (72 °C, 0.2 mm), and the product Kugelrohr distilled (110 °C, 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 (9 H, s), 2.71 (4 H, m), 3.46 (2 H, s), 3.68 (3 H, s), 5.72 (2 H, m), 8.9 (1 H, br). Anal. ($C_{14}H_{21}NO_4$) C, H, N.

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

Methyl 3-(5-*tert*-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 h) over 10% Pd/C (500 mg), the catalyst removed, and the solvent evaporated. The product (3.12 g, 84%) was Kugelrohr distilled (110 °C, 0.1 mm): NMR (CCl_4) δ 1.41 (9 H, s), 1.3–2.8 (12 H, m), 2.21 (3 H, s), 3.58 (3 H, s); MS *m/e* 285 (1.8, M^+), 198 (50), 142 (100). Anal. ($C_{15}H_{27}NO_4$) C, H, N.

Attempted Dieckmann Cyclization of 4b. The starting material, *tert*-butyl methyl ester **4b**, was added to a mixture of toluene, *tert*-butyl alcohol (10 mol %), and KH (110 mol %), refluxing 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** (mass spectrum, $FeCl_3$). Under the same conditions, methyl *tert*-butyl suberate cyclized to the *tert*-butyl β-keto ester in 55% yield.

Methyl (*E*)-β-(1-Methyl-2-pyrrolyl)acrylate (8). A mixture of 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 %) was stirred under N_2 at i.t. 70 °C for 35 h. Evolution of CO_2 was essentially complete after 25 h. Solvent was evaporated, followed by drying at 50 °C (5 mm) for 2 h. Distillation afforded some recovered aldehyde (80 °C, 2 mm) followed by the acrylate **8** (120 °C, 2 mm): 101 g, 77% yield based on starting material consumed; GC (180 °C) 2.5 min; NMR δ 3.66 (3 H, s, NCH_3), 3.71 (3 H, s, CO_2CH_3), 6.03 (1 H, d, J = 16 Hz, C=CH), 6.1 (1 H, m), 6.6 (1 H, m), 7.50 (1 H, d, J = 16 Hz, C=CH); MS *m/e* 165 (76, M^+), 134 (100, $M^+ - CH_3O$). Anal. ($C_9H_{11}NO_2$) C, H, N.

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 °C (2.5 mm) by Kugelrohr distillation; GC (180 °C) 1.0 min; NMR δ 2.74 (4 H, m, CH_2CH_2), 3.53 (3 H, s, NCH_3), 3.69 (3 H, s, CO_2CH_3), 5.9 (1 H, m), 6.05 (1 H, t), 6.55 (1 H, t); MS *m/e* 167 (18, M^+), 94 (100). Anal. ($C_9H_{13}NO_2$) C, H, N.

3-(1-Methyl-2-pyrrolyl)propanol (10). Crude methyl propanoate (**9**, 8.9 g, 53.2 mmol) was dissolved in 75 mL of 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 of ether over 0.5 h. After the mixture was stirred for 2 h more at 20 °C, to the reaction mixture were added 9 mL of H_2O and 4 mL of 10% NaOH. Removing the precipitate, then evaporating the solvent, afforded the propanol **10**: 6.7 g, 89% yield; GC (150 °C) 0.9 min, (200 °C) 0.25 min; bp 80–120 °C (1.1 mm) by Kugelrohr distillation; NMR δ 1.8 (1 H, br, OH), 1.85 (2 H, m), 2.65 (2 H, br t, J = 7 Hz), 3.54 (3 H, s, NCH_3), 3.70 (2 H, t, J = 6 Hz), 5.9 (1 H, m), 6.02 (1 H, t), 6.52 (1 H, t); MS *m/e* 139 (14, M^+), 94 (100). Anal. ($C_8H_{13}NO$) C, H, N.

3-(1-Methyl-2-pyrrolyl)propanol Methanesulfonate (11a). Crude propanol **10** (51 g, 367 mmol) was dissolved in 500 mL of CH_2Cl_2 and triethylamine (80 mL, 570 mmol, 155 mol %) was added. After the

mixture was cooled to 0 °C, methanesulfonyl chloride (37 mL, 48 mmol, 130 mol %, distilled) was added over 20 min. After 1 h of additional stirring at 0 °C, the mixture was washed with saturated NaCl, saturated Na_2CO_3, and saturated 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 °C (1.0 mm) by Kugelrohr distillation; NMR δ 2.1 (2 H, m), 2.7 (2 H, br t), 2.97 (3 H, s, OSO_2CH_3), 3.53 (3 H, s, NCH_3), 4.29 (2 H, t, J = 7 Hz), 5.85 (1 H, m), 6.02 (1 H, t), 6.52 (1 H, t); MS *m/e* 217 (7, M^+), 94 (100). Anal. ($C_9H_{15}NO_3S$) C, H, N.

2-(3-Iodopropyl)-1-methylpyrrole (11b). The crude methanesulfonate (**11a,** 81 g, 373 mmol) was dissolved in 550 mL of absolute ethanol and sodium iodide (112 g, 750 mmol, 200 mol %) was added. A mildly exothermic reaction ensued. After the solution was stirred for 20 h at 40 °C, the ethanol was evaporated, the residue was partitioned between ether and water, and the organic phase was evaporated, then Kugelrohr distilled to afford the iodide as a nearly colorless liquid: 51.5 g, 56% yield; GC (200 °C) 0.55 min; NMR δ 2.15 (2 H, m), 2.65 (2 H, br t), 3.22 (2 H, t, J = 7 Hz), 3.52 (3 H, s, NCH_3), 5.85 (1 H, m), 5.97 (1 H, t), 6.47 (1 H, t); MS m/e 249 (16, M^+), 94 (100). Anal. ($C_8H_{12}NI$) C, H, N.

Methyl 2-Methoxycarbonyl-5-(1-methyl-2-pyrrolyl)pentanoate (12). Sodium (9.5 g, 413 mmol, 187 mol %) was dissolved in 250 mL of methanol at 0 °C. Dimethyl malonate (50.5 mL, 442 mmol, 200 mol %) was added and the solution stirred at room temperature for 30 min. The propyl iodide (**11b,** 55 g, 221 mmol) in 150 mL of methanol was added and the solution was refluxed for 0.5 h, then cooled to 0 °C. A 1.0 M 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 °C, 0.2 mm) leaving the pyrrole malonate **12** (53.7 g, 96% yield), purified by Kugelrohr distillation: GC (200 °C) 2 min; TLC (Et_2O) 0.65, (Et_2O/petroleum ether, 1/1) 0.45; NMR δ 1.5–2.2 (4 H, m), 2.55 (2 H, br t), 3.40 (1 H, m), 3.50 (3 H, s, NCH_3), 3.73 (6 H, s, CO_2CH_3), 5.85 (1 H, m), 5.99 (1 H, t), 6.50 (1 H, t); MS *m/e* 253 (9, M^+), 94 (100). Anal. ($C_{13}H_{19}NO_4$) C, H, N.

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 °C, 12 h, 58.5 g, 424 mmol, 200 mol %) was suspended in 500 mL of ether and trichloroacetyl chloride (29 mL, 260 mmol, 125 mol %) was added, followed by the pyrrole malonate (**12,** 53.7 g, 212 mmol) in 100 mL of ether over 10 min. The mixture was stirred for 2 h, then filtered, extracted with saturated sodium bicarbonate, and dried to afford the trichloroacetyl derivative **13**: 82.5 g, 97.5% yield; mp 77–78 °C from petroleum ether; UV (CH_3OH) 322 nm (ϵ 15 000); TLC (Et_2O/petroleum ether, 1/1) 0.38; NMR δ 1.5–2.2 (4 H, m), 2.62 (2 H, br t), 3.37 (1 H, t), 3.71 (6 H, s, CO_2CH_3), 3.81 (3 H, s, NCH_3), 5.99 (1 H, d, J = 4.5 Hz), 7.31 (1 H, d, J = 4.5 Hz); 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 trichloroacetylpyrrole (**13,** 80 g, 200 mmol) was dissolved in 500 mL of acetone and 100 mL of water was added, followed by 1.00 M 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 an additional 10 min, the acetone and some of the water were evaporated, and the aqueous solution was extracted with ether. The product precipitated when 1 M HCl was slowly added to pH 3. After collection by filtration and drying, product (52 g, 88% yield) was obtained of mp 124–127 °C. Recrystallization from ethyl acetate gave pure pyrrole acid **14:** mp 142–144 °C; TLC (Et_2O) 0.5; UV (CH_3OH) λ_{max} 226 nm (ϵ 13 000); NMR δ 1.5–2.2 (4 H, m), 2.60 (2 H, br t), 3.37 (1 H, t), 3.72 (6 H, s, CO_2CH_3), 3.78 (3 H, s, NCH_3), 5.89 (1 H, d, J = 4.5 Hz), 6.98 (1 H, d, J = 4.5 Hz), 8.2 (1 H, br, CO_2H); MS *m/e* 297 (7, M^+), 280 (25, $M^+ - OH$), 94 (100). Anal. ($C_{14}H_{19}NO_6$) C, H, N.

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 of 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 the solution was washed 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 of CH_2Cl_2 in which was passed HCl(g) for 1 min, then cooled to 0 °C 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 °C dec; TLC ($CHCl_3/CH_3OH/NH_4OH$, 80/19/1) 0.35; NMR δ 1.2–2.5 (10 H, m), 2.91 (3 H, s, NCH_3), 3.0–4.4 (3 H, m), 3.73 (6 H, s, CO_2CH_3); IR 3400, 2940, 1720, 1620 cm^{-1}. Anal. ($C_{14}H_{24}NO_6Cl$) C, H, N.

5-[4,4-Bis(methoxycarbonyl)butyl]-3,4-dihydro-1-methyl-2*H*-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 (12 H, m), 3.52 (3 H, br s, NCH_3), 3.62 (6, H, s, CO_2CH_3), 8.48 (1 H, br s, N=CH).

Methyl 2-Methoxycarbonyl-5-(1-methyl-2-pyrrolidinyl)pentanoate (17). A. The crude iminium salt **16** (from 100 mg of **15,** 0.30 mmol) was cooled to 0 °C and dissolved in water (2 mL, pH 1.0), then hydrogenated (40 psi) over 20 mg of PtO_2 for 1 h. 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 6–9) 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 subjected to an acid–base partition followed by Kugelrohr distillation (120 °C, 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 °C) 1.6 min; NMR δ 1.1–2.1 (12 H, m), 2.26 (3 H, s, NCH_3), 3.0 (1 H, m), 3.34 (1 H, t), 3.70 (6 H, 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 °C and 0.5 mL of water was added with stirring. Saturated Na_2CO_3 was rapidly added to pH 9.8 at 20 °C, 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 °C, 0.1 mm) to afford bicyclomalonate **18** as a clear oil (18 mg, 24%): TLC ($CHCl_3/CH_3OH/NH_4OH$, 80/19/1) 0.75; GC (200 °C) 1.45 min; NMR δ 1.2–2.5 (10 H, m), 2.49 (3 H, s, NCH_3), 3.1 (1 H, m), 3.65 (3 H, s, CO_2CH_3), 3.68 (3 H, s, CO_2CH_3), 3.8 (1 H, m); MS *m/e* 255 (10, M^+), 224 (10, $M^+ - OCH_3$), 96 (50), 82 (100). Anal. ($C_{13}H_{21}NO_4$) C, H, N.

Methyl 9-Methyl-9-azabicyclo[4.2.1]nonane-2-carboxylate (21a). The bicyclic malonate (**18,** 98 mg) was dissolved in 6 M 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 17 h beneath a Soxhlet extractor filled with 3A molecular sieves. Evaporation of most of the solvent, basification with Na_2CO_3, and extraction into CH_2Cl_2 followed by Kugelrohr distillation (70–90 °C, 1.4 mm) afforded the bicyclo monoester **21a:** 40.1 mg, 53%; GC (200 °C) 0.65 min; NMR δ 1.2–2.5 (11 H, m), 2.40 (3 H, s, NCH_3), 3.1–3.5 (2 H, m), 3.65 (3 H, s, CO_2CH_3); MS *m/e* 197 (18, M^+), 82 (100). Anal. ($C_{11}H_{19}NO_2$) C, H, N.

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 °C for 1.5 h. 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 °C for 1 h. After cooling, excess $SOCl_2$ was evaporated and the acid chloride distilled at 100 °C (14 mm): 71 g, 79% yield; NMR δ 1.8–2.6 (4 H, m), 2.99 (2 H, t), 3.67 (3 H, s).

Methyl 4-(1-Methyl-2-pyrrolylcarbonyl)butanoate (23). The acid chloride of hydrogen methyl glutarate (**22,** 26.2 g, 154 mmol) was dissolved in 100 mL of 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 of CH_2Cl_2 at −40 °C, maintaining about i.t. −20 °C. After 15 min, 1.5 g more 1-methylpyrrole was added and stirring continued for 45 min at i.t. −25 °C and 1 h at 20 °C. The solvent was removed and 200 mL of ice and water added to the cooled mixture, which was extracted into ether (four times). The ether layer was washed with saturated

sodium carbonate solution and 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 °C) **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 °C, 0.4 mm): mp 37–39 °C; yield 16.5 g, 51%; NMR δ 2.2 (4 H, m), 2.79 (2 H, t), 3.61 (3 H, s, CO_2CH_3), 3.88 (3 H, s, NCH_3), 6.01 (1 H, dd), 6.68 (1 H, m), 6.86 (1 H, dd). Anal. ($C_{11}H_{15}NO_3$) C, H, N.

Methyl 4-(1-methyl-3-pyrrolylcarbonyl)butanoate (24) was the *major component of the higher boiling fraction*, 7.1 g (22%), bp 165 °C (0.1 mm). A sample was purified by chromatography on silica gel, eluting with ether: NMR δ 2.2 (4 H, m), 2.72 (2 H, t), 3.61 (6 H, s, $NCH_3CO_2CH_3$), 6.48 (2 H, d, J = 2 Hz), 7.17 (1 H, 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 °C for 15 min. Potassium hydroxide (24 g, 430 mmol, 430 mol %) was added slowly and the bath temperature raised slowly (1.5 h) to 210 °C, removing the water and excess hydrazine by distillation. Heating at i.t. 190 °C was continued for 4.5 h, the solution was cooled, acidified to pH 2.0, extracted with ether (five times), and dried, and the ether was evaporated to afford essentially pure acid **25** as a light yellow solid, mp 58–61 °C, 17.9 g (100% yield). Kugelrohr distillation (110 °C, 0.2 mm) afforded white crystals: mp 71–73 °C; NMR δ 1.7 (4 H, m), 2.4 (4 H, m), 3.46 (3 H, s, NCH_3), 5.80 (1 H, t), 6.41 (1 H, t). Anal. ($C_{10}H_{15}NO_2$) C, H, N.

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 of hot water; 10 min after homogeneity was achieved, the water was evaporated and the product further dried in a vacuum desiccator for 24 h, yielding the lithium salt of **25** (17.9 g, 97% yield).

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

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 h 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 δ 1.7 (4 H, m), 2.16 (3 H, s, $COCH_3$), 2.55 (4 H, m), 3.87 (3 H, s, NCH_3), 6.05 (1 H, d), 7.47 (1 H, d).

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

6-(5-Methoxycarbonyl-1-methyl-2-pyrrolidinyl)-2-hexanol (29). The pyrrole keto ester (**28**, 7.84 g, 33.2 mmol) was dissolved in 50 mL of methanol and a solution of sulfuric acid (5.6 mL, 100 mmol, 300 mol %) in 50 mL of methanol was added. The solution was hydrogenated (40–50 psi) over 5% rhodium on alumina (7.84 g) for 44 h, monitoring the progress of the reduction by UV. After the catalyst was removed, the solvent was evaporated, water was added, the pH was adjusted to 1.5–2.0, and the aqueous solution was extracted twice with ether. The aqueous phase was then adjusted to pH 9.8 with saturated Na_2CO_3 and extracted four times with CH_2Cl_2. After drying and evaporation of the solvent, the crude product (7.5 g) was Kugelrohr distilled (110 °C, 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 °C) 1.7 min; NMR δ 1.16 (3 H, d, $HOCCH_3$), 1.1–2.3 (15 H, m), 2.30 (3 H, s, NCH_3), 2.96 (1 H, br t), 3.69 (3 H, s, CO_2CH_3). Anal. ($C_{13}H_{25}NO_3$) C, H, N.

6-(5-Methoxycarbonyl-1-methyl-2-pyrrolidinyl)-2-hexanone (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 of acetone, 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 four times with CH_2Cl_2, the organic extract was dried and evaporated, and the product was purified by Kugelrohr distillation (90–100 °C, 0.15 mm): yield 2.30 g, 88%; TLC ($CHCl_3/CH_3OH/NH_4OH$, 90/9.5/0.5) 0.7; GC (200 °C) 1.7 min, coinjects with **29**; NMR δ 1.1–2.6 (13 H, m), 2.11 (3 H, s, $COCH_3$), 2.32 (3 H, s, CO_2CH_3), 2.97 (1 H, br t), 3.71 (3 H, s, CO_2CH_3). Anal. ($C_{13}H_{23}NO_3$) C, H, N.

6-(5-Carboxy-1-methyl-2-pyrrolidinyl)-2-hexanone Hydrochloride (30b). The methyl ester (**30a**, 1.94 g, 8.05 mmol) was dissolved in 6 M HCl (9.7 mL, 58 mmol, 720 mol %) and heated to 90 °C for 30 min under nitrogen. Excess HCl and water were removed (50 °C, 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 (12 H, m), 2.18 (3 H, s, $COCH_3$), 2.94 (3 H, s, NCH_3), 3.3 (1 H, m), 4.22 (1 H, br t). Anal. ($C_{12}H_{22}NO_3Cl$) C, H, N.

3,4-Dihydro-1-methyl-5-(5-oxohexyl)-2*H*-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 °C. 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 (11 H, m), 2.05 (3 H, s, $COCH_3$), 3.56 (3 H, br s, NCH_3), 4.3 (1 H, m), 8.6 (1 H, br s, N=CH).

6-(1-Methyl-2-pyrrolidinyl)-2-hexanol (32). A. The crude iminium salt **31** (from 31 mg of **30b**, 0.12 mmol) was dissolved in water (1 mL, pH 0.5) and hydrogenated (50 psi, 1 h) 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 h) over PtO_2 (20 mg). Partition between aqueous alkali and CH_2Cl_2 afforded **32**: yield 85 mg, 75%; GC (200 °C) 0.65 min; NMR δ 1.18 (3 H, d), 1.2–2.3 (16 H, m), 2.29 (3 H, s, NCH_3), 2.86 (1 H, s, OH), 3.0 (2 H, m), 3.67 (1 H, 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 °C) 0.65 min; NMR δ 1.2–2.6 (13 H, m), 2.12 (3 H, s, $COCH_3$), 2.29 (3 H, s, NCH_3), 3.0 (2 H, 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 of methanol, and heated to reflux for 16 h. The mixture then was cooled, the methanol was evaporated and replaced with water, and the acidic aqueous solution was extracted twice with ether to remove trimethyl phosphate, then basified to pH 10 with saturated sodium carbonate and extracted four times with CH_2Cl_2. After drying and evaporation of solvent, the crude product (1.07 g) obtained was purified by Kugelrohr distillation (60–65 °C/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 °C) 0.75 min; IR 3400, 2920, 1705 cm^{-1} (lit.[5] 1705 cm^{-1}); NMR δ 1.3–2.5 (11 H, m), 2.12 (3 H, s, $COCH_3$), 2.39 (3 H, s, NCH_3), 3.3 (2 H, 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. ($C_{11}H_{19}NO$) C, H, N.

The product was stored at 0 °C 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 h at pH 10. The hydrochloride of **34** was an extremely hygroscopic, white powder: mp 121–125 °C (lit.[5] mp 152–155 °C); single enantiomer, NMR δ 2.22 (3 H, s, $COCH_3$), 2.90 (3 H, s, NCH_3) [lit. δ 2.22 (3 H, s), 2.91 (3 H, s)]; $LD_{50} > 25$ mg/kg (ip, mouse).

B. Ester **21a** (6.6 mg, 0.0335 mmol) was hydrolyzed in 0.1 M aqueous LiOH (105 mol %) for 1 h, then dried (60 °C, 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 h. 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 °C) 1.1 (80%), 1.25 (15%), 1.8 (5%) min; NMR δ 1.2–2.5 (11 H, m), 2.15 (3 H, s, $COCH_3$), 4.2–4.8 (2 H, m), 4.78 (2 H, 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 0.1 M 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 (11 H, m), 2.23 (3 H, s, $COCH_3$), 4.2 (2 H, m); LD_{50} = 2.5 mg/kg (ip, mouse).

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Deuterium-Induced Differential Isotope Shift ^{13}C NMR. 1. Resonance Reassignments of Mono- and Disaccharides[1]

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Abstract: Previous assignments of natural-abundance ^{13}C NMR chemical shifts of mono- and disaccharides have been reevaluated by use of a newly developed differential isotope shift (DIS) technique. Deuterium-induced ^{13}C isotope shifts were produced through rapid interchange of carbohydrate hydroxyl groups in a D_2O environment. The differential shift positions (D_2O vs. H_2O environments) were measured simultaneously in the magnetic field with a dual coaxial NMR cell. Each isotopic chemical shift position was sharply defined because of rapid OH and OD interchange in the separate, respective solvent environments. The largest induced upfield displacements due to deuterium substitution of OH were noted for those carbons bearing hydroxyl groups, β shifts (0.14 ppm). β shifts at C-1 were smaller (0.11 ppm) than all other β induced shifts. Shifts due to vicinal OD, γ shifts, were ~0.03–0.06 ppm and additive. Differences in induced γ shifts directed from cis vs. trans hydroxyl groups at C-1 were found to be statistically significant. Isotope shift parameters were calculated from a linear regression analysis of data compiled from 12 structurally different pyranose structures. These parameters were used to calculate the isotope shifts for other pyranose and furanose mono- and disaccharides. DIS analysis was also applied to different substituted carbohydrates in both aqueous and nonaqueous systems as well as α- and β-D-glucuronopyranoses.

^{13}C NMR spectroscopy is becoming more important as a tool for studying the structural interactions of low molecular weight carbohydrates,[2-4] oligosaccharides, polysaccharides,[5-9] and antigenic polysaccharides.[10,11] In all such studies it is imperative that the correct assignment of the ^{13}C resonances be unambiguous. Several strategies have been applied to assist in making unequivocal assignments.[12] Early studies[13-15] with continuous-wave instrumentation relied heavily on analogies to available data of model compounds. With the advent of pulsed Fourier transform instrumentation, techniques such as spin-lattice relaxation,[2] off-resonance decoupling, selective heteronuclear decoupling, and long-range ^{13}C–H coupling[12] became viable alternatives. Unfortunately these methods are in many cases difficult to perform, i.e., they require large