Synthesis of 3-Dienoyl Tetramic Acids Related to Streptolydigin and Tirandamycin[1,2]

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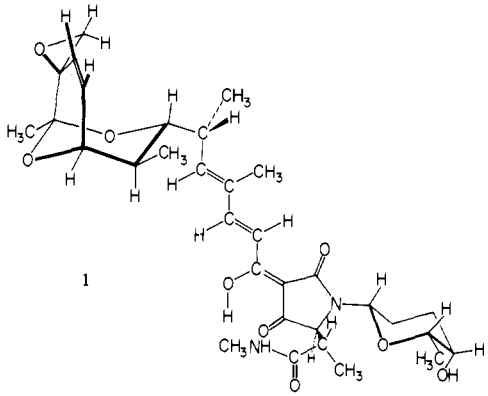
Abstract: 3-Dienoyl tetramic acids related to the antibiotics tirandamycin and streptolydigin have been prepared via intramolecular Claisen condensation and via acylation of 2,4-pyrrolidiones. The spectroscopic properties of these novel analogues, which are described, provide excellent models for like properties of the antibiotics.

Publications from this laboratory have established the structures of the antibiotics streptolydigin (**1**)[2,3] and tirandamycin (**2**)[2,4] as complex 3-dienoyl tetramic acids. Streptolydigin is of interest for its antimicrobial activity,[5a] its inhibition of bacterial DNA-directed RNA polymerase,[6a-f] its effect on the replication of Col El plasmid DNA in *E. coli*,[7a] and its recently discovered selective inhibition of terminal deoxynucleotidyl transferase from leukemic cells.[7b] Tirandamycin has similar antimicrobial[5b] and bacterial RNA polymerase inhibitory[6g] activities. The antibacterial and bacterial polymerase inhibitory activities of these two antibiotics can be contrasted with the antineoplastic activity demonstrated by simpler 3-acyl tetramic acids and their derivatives,[8] including tenuazonic acid.[8a,9] One possibility for the differing activities lies in the 2,9-dioxabicyclo[3.3.1]nonane system common to **1** and **2**; another in the dienoyl unit of **1** and **2**.



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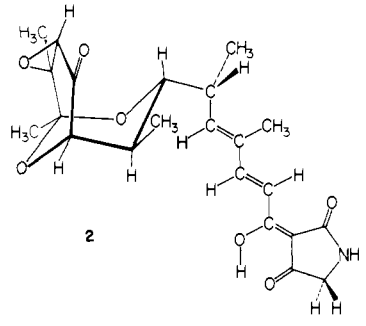

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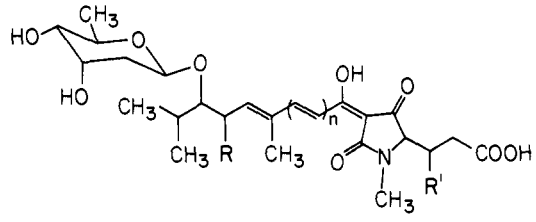
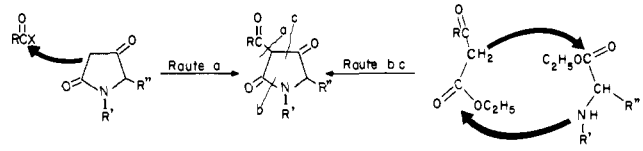
To test the hypothesis that the dienoyl unit is important for antibacterial and bacterial RNA polymerase inhibitory activities, we have prepared a number of 3-dienoyl tetramic acids. In addition to providing substrates for biological and enzymatic studies these tetramic acids serve as useful models for comparison to the unique ultraviolet spectral behavior of **1** and **2** and for assistance in the assignment of the antibiotics' carbon magnetic resonance (^{13}C NMR) spectra. The routes developed for the synthesis of the models should also prove useful in any eventual synthesis of streptolydigin and tirandamycin or of the related 3-polyenoyl tetramic acids α-lipomycin (**3**)[10] and oleficin (**4**),[11] which are also antimicrobial agents.



3: R = CH_3, R' = H, n = 4

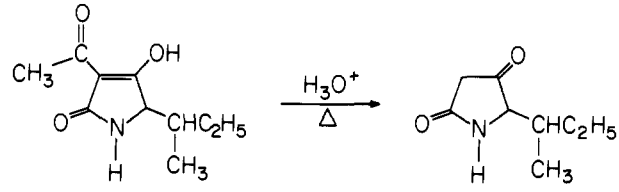
4: R = H, R' = CH_3, n = 5

The most straightforward route to the 3-acyl tetramic acid system (route a) involves acylating the enolate of a tetramic acid (2,4-pyrrolidione). The 2,4-pyrrolidiones and dienoyl



halides should be readily accessible and the route might be applicable to the synthesis of tirandamycin and streptolydigin themselves or of a hybrid of the two, since the dienoic acids tirandamycic acid[4] and streptolic acid[12] are periodate degradation products of the antibiotics. A second attractive route (route bc, which has been used for the synthesis of simple 3-acetyl tetramic acids)[13a] involves condensation of an ester (β-keto ester) with an amine (α-amino acid ester) and subsequent intramolecular Claisen condensation. Both routes have been employed in the present study.

Acylation of Tetramic Acids. 1-Methyl-2,4-pyrrolidione-5-(*N*-methylacetamide) (**5**) was chosen as a model tetramic acid for streptolydigin and was prepared in 22–25% overall yield in five steps from diethyl maleate (Figure 1), via diethyl *N*-methyl-DL-aspartate (**6**, prepared from diethyl maleate and methylamine in 85% yield), 3-acetyl-1-methyl-2,4-pyrrolidione-5-(ethyl acetate) (**7**),[14] and 1-methyl-3-(1-methylaminoethylidene)-2,4-pyrrolidione-5-(*N*-methylacetamide) (**8**). Precedence for the hydrolysis of **8** to the pyrrolidione **5** was provided by Stickings during the structure elucidation of tenuazonic acid (**9**), which on acidic hydrolysis gave



9 **10**

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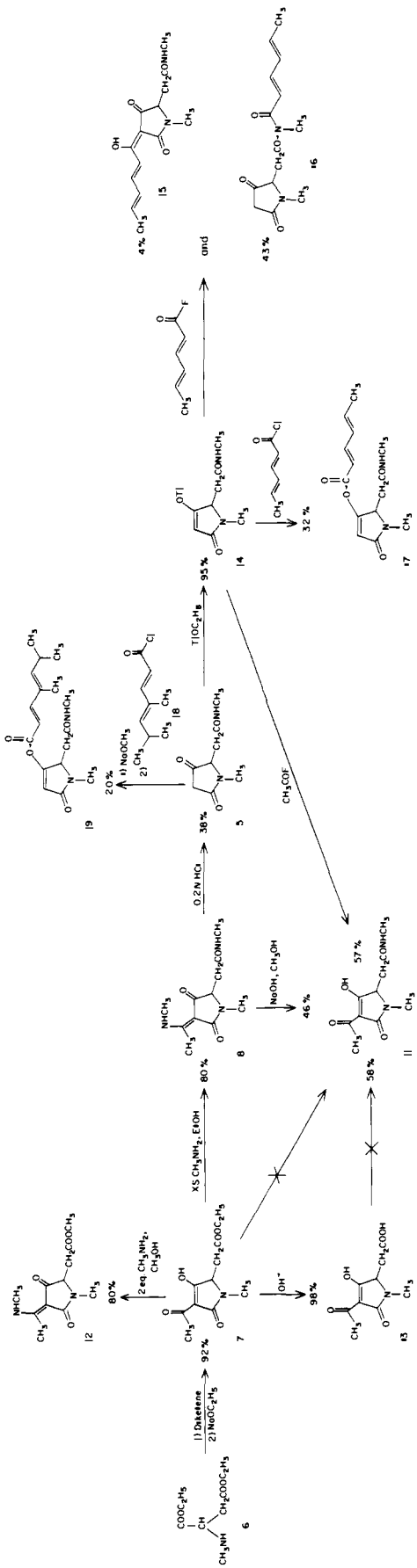


Figure 1. Synthesis of 1-methyl-2,4-pyrrolidione-5-(*N*-methylacetamide) (**5**) and its reactions with acyl halides.[14]

deacetyltenuazonic acid (5-*sec*-butyl-2,4-pyrrolidione) (**10**).[13b]

In view of Stickings' hydrolysis of **9** to **10** our initial goal was the conversion of **7** to the *N*-methylamide **11,** whose acetyl group we planned to remove to give **5.** However, attempts to form **11** with limited amounts (2 equiv) of methanolic methylamine gave instead the enamine **12,** while attempts to prepare **11** via coupling of the acid **13** with methylamine employing dicyclohexylcarbodiimide or thionyl chloride also were unsuccessful. Although **11** could be prepared from **8** in refluxing methanolic sodium hydroxide, the conversion of **11** to **5,** involving an additional step over the direct conversion of the enamine **8** to **5,** was not further investigated.

Acyl fluorides and the thallium salt (**14**) of **5** were chosen for acylation of **5,** since Taylor, Hawks, and McKillop have reported that thallium(I) enolates derived from 1,3-dicarbonyl systems reacted with acyl fluorides (0 °C) and acyl chlorides (−78 °C) to give C- and O-acylation products, respectively. The models described[15] are admittedly imperfect for the present study, since neither pyrrolidiones nor dienoyl fluorides had been tested.

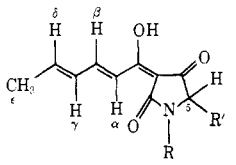
Treatment of **5** with thallous ethoxide in dry dimethylformamide gave the analytically pure thallium(I) enolate (**14**) (Figure 1) and subsequent treatment of **14** with acetyl fluoride in dry dimethylformamide gave in 57% yield 3-acetyl-1-methyl-2,4-pyrrolidione-5-(*N*-methylacetamide) (**11**),[14] whose spectral and physical properties were identical with those of the product obtained from alkaline hydrolysis of **8.** Thus, the pyrrolidione behaved in the desired manner with acetyl fluoride.

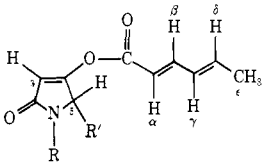
On the other hand, acylation of enolate **14** with sorbyl fluoride[16] gave two products, both with the expected molecular weight 278, as established by their mass spectra. The minor fraction (**15,** 4% yield) and the major fraction (**16,** 43% yield) gave respectively positive and negative responses to ferric chloride spray reagent.[17] The product obtained in lower yield was assigned the structure of the desired 1-methyl-3-sorbyl-2,4-pyrrolidione-5-(*N*-methylacetamide) (**15**)[14] on the basis of its positive ferric chloride response. Moreover, its ultraviolet spectrum showed the expected and unusual hypsochromic shift exhibited by streptolydigin and tirandamycin on changing from acidic to basic solution (see Table II). The product obtained in large yield was assumed at first to be the 4-*O*-acyl derivative (**17**) of **5.** However, it showed an infrared carbonyl absorption at 1700 cm^{-1} (acyclic imide), while the expected O-acylation product (**17**) should have an absorption between 1740 and 1750 cm^{-1}. The ^1H NMR spectrum (100 MHz) of this material (Table I) showed two *N*-methyl singlets, at δ 2.80 and 2.85, whereas that of the *N*-methylamide **15** showed a singlet and a doublet. The spectral data thus indicate the major product of the thallium acylation reaction to be the *N*-acyl derivative **16.**

In a second experiment, the authentic O-acylation product **17** was prepared by acylation of the thallium salt **14** with sorbyl chloride. The *O*-acyl product (**17**) showed an *N*-methyl doublet (δ 2.77) and an *N*-methyl singlet (δ 2.99) in its ^1H NMR spectrum (100 MHz), and its infrared spectrum showed the expected carbonyl absorption at 1737 cm^{-1}, appropriate for an unsaturated acylated enol. Thus, while acetylation of the thallium enolate (**14**) was successful, acylation with an unsaturated acyl fluoride was far less successful.

Attempts to use other metal salts of **5** were even less successful. Sorbyl chloride and 4,6-dimethyl-(*E,E*)-2,4-heptadienoyl chloride (**18;** cf. Figure 3 for synthesis) were condensed with the sodium, ethoxymagnesium, and lithium enolates of pyrrolidione **5.** In each case, the product showed carbonyl absorption at 1735 cm^{-1} attributable to the unsaturated acylated enol and gave a negative ferric chloride response. Their structures were assigned as the O-acylation products **17** and

Table I. ^{1}H NMR Spectral Data for C- and O-Acylation Products





Compd[a]	R	R′	3-H	5-H	ε-CH_3	α-H	β-H	γ-H	δ-H	Other protons
C-Acyl										
15[b,c]	CH_3	C_3H_6NO[g]		3.86 (m)	1.82 (bd)	5.76 (d)	7.30 (m)	6.15 (m)	6.15 (m)	2.74, 2.81 (NCH_3) (s), 2.75 ($CHCH_2$) (m)
39	C_7H_7[g]	H		3.58 (s)	1.88 (bd)	7.07 (d)	7.28 (m)	6.35 (m)	6.35 (m)	4.61 ($ArCH_2$) (s), 7.30 (ArH) (s)
40[d]	CH_3	H		3.60 (s)	1.92 (d)	7.10 (d)	7.15 (dq)			2.99 (NCH_3) (s)
41	CH_3	H		3.70 (s)	1.90 (bd)	7.05 (d)	7.41 (m)	6.27 (m)	6.27 (m)	3.00 (NCH_3) (s), 12.60 (OH) (s)
56	C_6H_{11}[g]	H		3.65 (s)	1.87 (bd)	7.04 (d)	7.38 (m)	6.31 (m)	6.31 (m)	1.60 [$-(CH_2)_5-$] (m), 4.05 (CH) (m)
57	C_8H_9O[g]	H		3.56 (s)	1.91 (bd)	7.15 (d)	7.44 (m)	6.30 (m)	6.30 (m)	4.53 ($ArCH_2$) (s), 3.66 (OCH_3) (s), 6.85, 7.19 (ArH) (AB quartet)
58[e]	C_8H_9O[g]	H		3.56 (s)		7.08 (d)	7.49 (d)		5.87 (bd)	1.01 [$(CH_3)_2CH$] (d), 1.88 ($CH_3C=$) (d), 2.74 (CH) (m), 3.76 (CH_3O) (s), 4.53 ($ArCH_2$) (s), 6.86, 7.16 (ArH) (AB quartet)
59[f]	H	H		4.26 (s)	2.05 (bd)	7.12 (d)	7.88 (m)	6.56 (m)	6.56 (m)	
O-Acyl										
17	CH_3	C_3H_6NO[g]	5.22 (bs)	6.53 (m)	1.83 (bd)	5.69 (d)	7.24 (m)	6.16 (m)	6.16 (m)	2.38 (bd, 1 H), ~2.90 (m, 1 H) (CH_2CH), 2.77 ($NHCH_3$) (d), 2.99 (NCH_3) (s), 5.91 (NH) (m)
19[c,e]	CH_3	C_3H_6NO[g]	6.05 (bs)	4.57 (m)		5.78 (d)	7.43 (d)		5.85 (bd)	0.99 [$(CH_3)_2CH$] (d), 1.76 ($CH_3C=$) (bd), 2.48 (CH_2CH) (m), 2.83 ($NHCH_3$) (m), 2.86 (NCH_3) (s), 4.57 [$(CH_3)_2CH$] (m)
34	C_7H_7[g]	H	5.98 (t)	4.00 (d)	1.90 (d)	5.87 (m)	7.12 (dq)			4.62 ($ArCH_2$) (s), 7.29 (ArH) (s)
35	C_7H_7[g]	H	6.00 (t)	3.97 (d)	1.86 (bd)	5.76 (d)	7.24 (m)	6.27 (m)	6.27 (m)	4.63 ($ArCH_2$) (s), 7.27 (ArH) (s)
36[d]	CH_3	H	5.86 (t)	4.08 (d)	1.92 (d)	5.89 (m)	7.14 (dq)			2.98 (NCH_3) (s)
37	CH_3	H	5.92 (t)	4.08 (d)	1.93 (bd)	5.79 (d)	7.39 (m)	6.20 (m)	6.20 (m)	2.96 (NCH_3) (s)

[a] $CDCl_3$ solution, 100 MHz except as noted. [b] CD_3OD solution. [c] 60 MHz. [d] Acyl group: (*E*)-$CH_3CH{=}CHCO-$. [e] Acyl group: (*E,E*)-$CH_3CH(CH_3)CH{=}C(CH_3)CH{=}CHCO-$. [f] Trifluoroacetic acid solution. [g] C_7H_7 = $C_6H_5CH_2$; C_3H_6NO = $CH_2CONHCH_3$; C_8H_9O = *p*-$CH_3OC_6H_4CH_2$; C_6H_{11} = cyclohexyl.

19, respectively. Varying the solvent system also did not give any of the desired 3-dienoyl tetramic acids.

Synthesis of a tirandamycin-like system via the thallium acylation route requires preparation of a 2,4-pyrrolidione unsubstituted at C-5 and also unsubstituted at N-1; i.e., **20** (Figure 2). Although **20** is in principle derivable from acidic hydrolysis of the corresponding 3-acetyl tetramic acid **21,**[14] the 2,4-pyrrolidione produced in that reaction underwent self-condensation during hydrolysis to form the "dimeric bis(pyrrolidione)" **22,**[14] a reaction observed previously by Mulholland[18] et al., who reported that selected 2,4-pyrrolidiones could be obtained in high yields by boiling the corresponding 3-carbethoxytetramic acids in water for 5 min, but that prolonged heating resulted in formation of the dimers. The earlier authors[18] reported that the dimers gave an intense purple coloration with ferric chloride reagent, while freshly prepared 2,4-pyrrolidiones gave only a faint brown ferric chloride coloration.

Since hydrolysis of the acetyl tetramic acids gave dimers, we turned to the 3-carbethoxytetramic acid precursor (**23,**[14] prepared in two steps from glycine ethyl ester, Figure 2) for the preparation of **20.** Hydrolysis of **23** gave the 2,4-pyrrolidione **20** in reasonable yield. Treatment of freshly prepared **20** with thallous ethoxide gave the desired enolate salt (**24**)[14] in quantitative yields, but the salt was unstable above 35 °C and oxygen sensitive.

Attempts to prepare the benzyl- and *N*-methylpyrrolidiones (**27, 28**) by hydrolysis of the 3-acetylpyrrolidiones (**29, 30**)[14] also gave dimers (**31a,b**),[14] but **27** and **28** could be prepared in good yield from the 3-carbethoxypyrrolidiones (**32, 33**)[14] and converted to the thallium salts (**25, 26**), which were stable. Acylation of **25** and **26**[14] with sorbyl fluoride and crotonyl fluoride gave nearly exclusively O-acylation products (**34–37**), together with small amounts of the desired C-acylation products (**40, 41**)[14] from the *N*-methyl enolate (**26**).

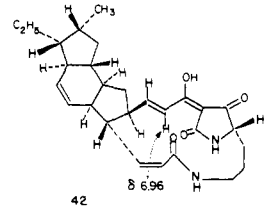
The ^{1}H NMR spectra of the C- and O-acylation products reveal significant differences between the isomeric pairs. As shown in Table I, the O-acylation products show triplets at-

Table II. Ultraviolet Spectra of 3-Dienoyl Tetramic Acids, 3-Acetyl Tetramic Acids, and Ethyl Dienoylacetates

Compd	Solvent[a]	λ_{max}, nm (ϵ_{max})			λ_{shd}, nm (ϵ_{shd})
		Dienoyl Tetramic Acids			
1	A	347 (27 100)		250 (11 350)	368 (22 000)
	B	334 (22 600)	289 (19 100)	261 (16 500)	
	C	355 (37 200)		242 (10 000)	368 (35 800)
22	A	352 (31 500)		241 (13 000)	367 (26 700)
	B	333 (22 100)	287 (21 600)	255 (18 900)	
	C	354 (40 000)		238 (11 800)	368 (36 400)
15	A	339 (16 700)	285 (12 900)		
	B	338 (15 200)	284 (15 950)	262 (18 100)	
	C	356 (22 600)		241 (10 400)	373 (20 400), 343 (21 100)
41	A	358 (27 500)		238 (13 100)	374 (22 100)
	B	337 (17 000)	280 (18 000)	259 (18 750)	
	C	353 (29 100)		237 (13 250)	373 (29 100)
39	A	338 (14 200)		261 (14 400)	
	B	340 (14 300)		261 (14 000)	
	C	358 (27 500)		238 (7500)	372 (23 500)
56	A	359 (21 000)		243 (7500)	372 (16 200)
	B	341 (14 300)	280 (13 700)	261 (15 000)	
	C	359 (27 700)		242 (8000)	
57	A	353 (26 100)			370 (19 600)
	B	337 (18 900)		261 (19 700)	275 (18 200), 281 (17 800)
	C	359 (37 500)		228 (15 300)	372 (32 000), 241 (11 500)
58	A	340 (16 200)	284 (12 300)	264 (11 600)	374 (8400)
	B	336 (16 900)	284 (13 900)	263 (13 400)	
	C	361 (31 000)	246 (7200)	229 (12 100)	378 (28 800)
59	A	351 (22 800)		235 (7200)	366 (17 400)
	B	330 (15 100)	281 (14 100)	254 (12 100)	
	C	352 (29 800)		233 (7900)	
		Acetyl Tetramic Acids			
29	A			281 (11 250)	244 (8900)
	B			282 (14 800)	239 (15 200)
	C			281 (10 750)	
30	A			282 (10 750)	244 (7700)
	B			282 (12 000)	242 (11 800)
	C			281 (10 000)	223 (5700)
		Ethyl Dienoylacetates			
44	A		283 (20 300)		
	B	331 (17 000)	268 (17 100)		
	C		284 (20 000)		
45	A		288 (16 000)		
	B	335 (14 000)	274 (13 200)		
	C		290 (15 800)		

[a] A = 95% ethanol; B = 0.009 N KOH in ethanol; C = 0.009 N H_2SO_4 in ethanol.

tributed to the olefinic H-3 at δ 5.9–6.0 ($J \leq 1$ Hz). Other differences were observed in the H-5 proton(s) of the ring and the α-olefinic protons of the α,β-unsaturated acyl unit. In the O-acylation products, the H-5 methylene protons (δ 3.9–4.1) are deshielded by ca. 0.4 ppm relative to the H-5 protons of the *C*-acyl isomers (δ 3.5–3.7). By contrast, the α-olefinic protons (δ 7.0–7.2) of the *C*-acyl isomers are deshielded substantially (ca. 1.3 ppm) relative to the α protons of the *O*-acyl isomers (δ 5.7–5.9). Similar arguments can be advanced to explain both phenomena. In the *O*-acyl isomers, the H-5 protons are in the deshielding zone of the enol ester carbonyl group. This effect is even more pronounced for the isomeric pair 1-methyl-3-sorbyl-2,4-pyrrolidione-5-(*N*-methylacetamide) (**15**)[14] and 1-methyl-4-sorbyloxy-3-pyrrolin-2-one-5-(*N*-methylacetamide) (**17**), in which the H-5 methine protons appear at 3.95 and 6.53 ppm, respectively. In the *C*-acyl isomers, the α-olefinic proton is in the deshielding zone of the lactam carbonyl group. Related natural products exhibiting the same deshielding effect of the ring carbonyl are ikarugamycin (**42**)[19] and aspertetronin A (**43**),[20] in which the α-olefinic protons are found at δ 6.96 and 7.32, respectively.



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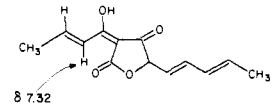

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Cyclization of α-Acylacetamido Esters. The low yields of C-acylation products obtained by the thallium acylation route suggested further exploration of the intramolecular Claisen condensation route. Lacey[13] utilized this approach in the synthesis of a series of 3-acetyl tetramic acids, and Folkers et al.[21] later synthesized tenuazonic acid (**9**) from L-isoleucine by this route. In earlier work the intermediates were obtained by acylation of the appropriate α-amino acid esters with diketene; however, substituted diketenes are chemically unavailable and dienoylacetyl esters were investigated as acylating agents for the present study. The dienoylacetyl esters used as model compounds, ethyl 3-oxo-(*E,E*)-4,6-octadienoate (**44**) and ethyl 6,8-dimethyl-3-oxo-(*E,E*)-4,6-nonadienoate (**45**), were prepared from the corresponding dienoic acids as shown in Figure 3. For the latter ester the dienoic acid **46** was prepared in 15% overall yield in five steps from isobutyraldehyde, via 2,4-dimethyl-(*E*)-2-pentenoate (**47**, separated from

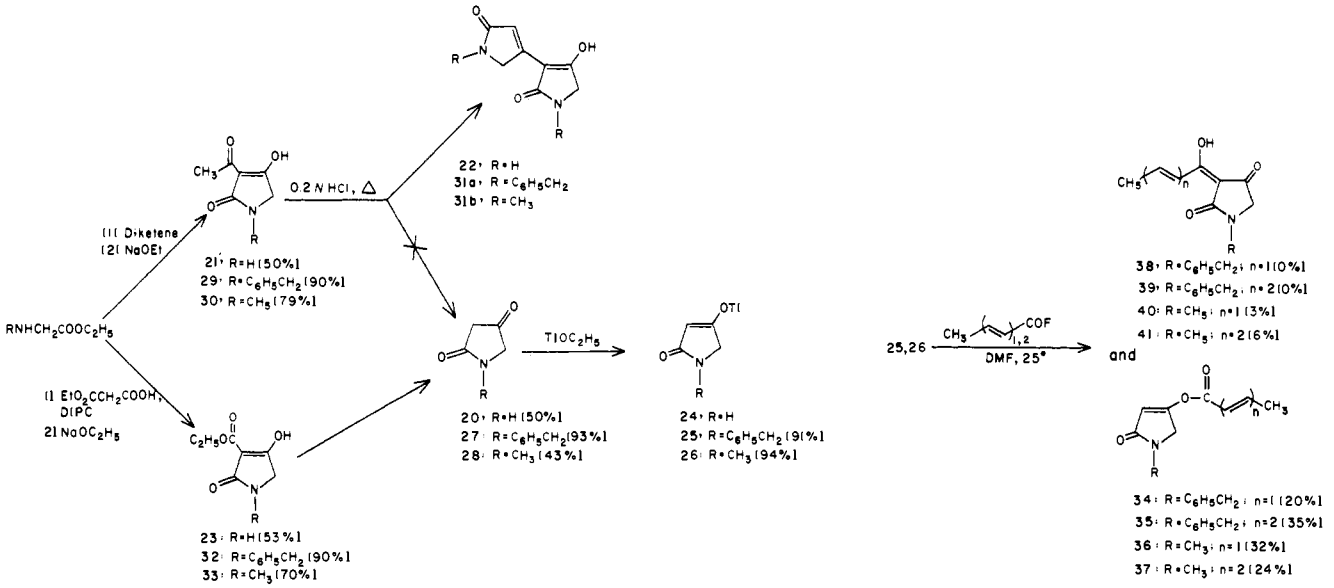


Figure 2. Preparation and acylation of 5-unsubstituted 2,4-pyrrolidiones (**20, 27, 28**).[14]

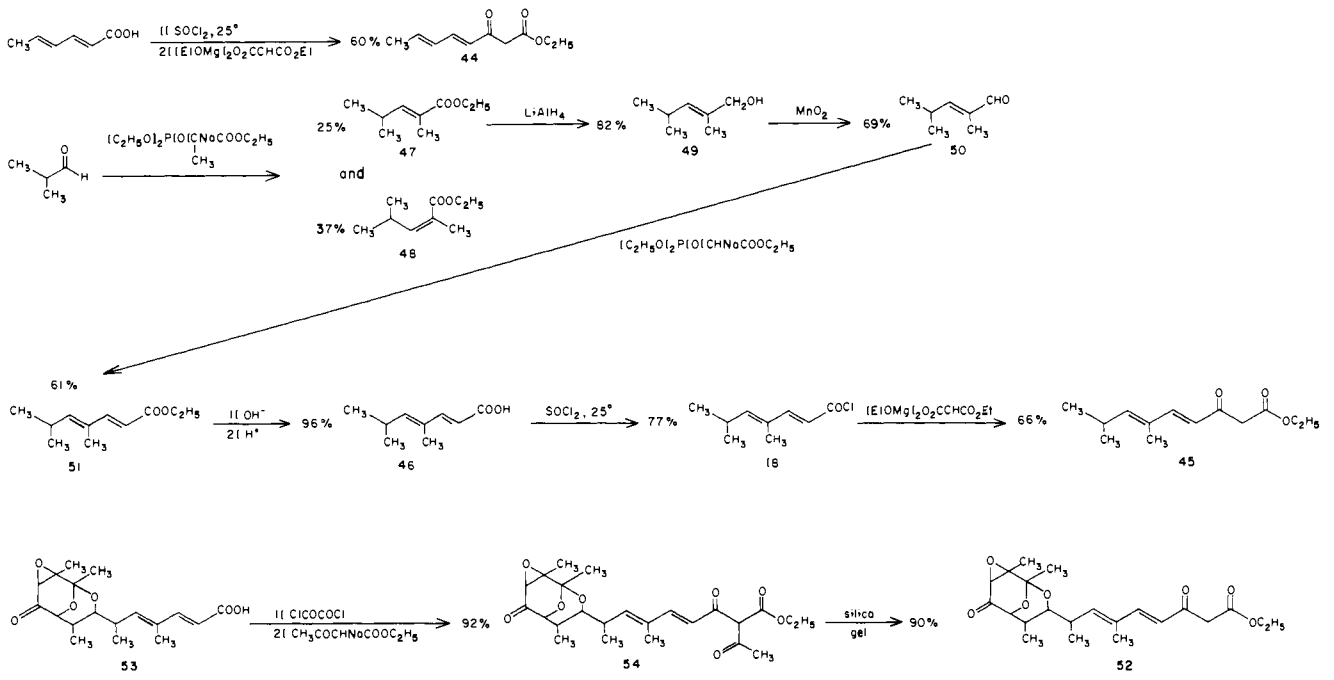


Figure 3. Preparation of dienoyl acetates (**44, 45, 52**).

the *Z* isomer **48** by spinning band distillation), 2,4-dimethyl-(*E*)-2-penten-1-ol (**49**), 2,4-dimethyl-(*E*)-2-pentenol (**50**), and ethyl 4,6-dimethyl-(*E,E*)-2,4-heptadienoate (**51**). Conversion of the dienoic acids to the acyl chlorides was accomplished with thionyl chloride at 25 °C, a temperature at which isomerization of the Δ^2 double bond of **46** was minimized (5%).

Condensation of the dienoyl chlorides with the di(ethoxymagnesio) enolate of monoethyl malonate followed by decarboxylation afforded the dienoylacetyl esters **44** and **45** in better than 60% yields. A more complex β-keto ester (**52**) was prepared from tirandamycic acid (**53**), obtained by periodate oxidation of tirandamycin (**2**). Treatment of **53** with oxalyl chloride followed by ethyl sodioacetoacetate, afforded acylacetoacetate **54**, which on deacetylation on silica gel gave **52** (Figure 3).

Condensation of the dienoylacetyl esters **44** and **45** with ethyl *N*-benzylglycinate, ethyl *N*-(4-methoxybenzyl)glycinate, or ethyl *N*-cyclohexylglycinate followed by Claisen cyclization gave the desired 3-dienoyl tetramic acids **39, 56, 57,** and **58**[14] in 25–45% yields (Figure 4), but attempts to condense ethyl tirandamycylacetate (**52**) with ethyl *N*-benzylglycinate resulted in thermal decomposition of the β-keto ester (**52**). Removal of the benzyl groups of the substituted tetramic acids was studied under solvolytic conditions.[22] Although treatment of 1-benzyl-3-sorbyl-2,4-pyrrolidione (**39**) with trifluoroacetic acid for 96 h at 25 °C gave a dark tar, similar treatment of 1-(*p*-methoxybenzyl)-3-sorbyl-2,4-pyrrolidione (**57**) gave 3-sorbyl-2,4-pyrrolidione (**59**) in 75–80% yield (Figure 4).[14]

Heating the sterically hindered ester *tert*-butyl sarcosinate at 110 °C in xylene with β-keto ester **44** gave a 51% yield of *tert*-butyl *N*-methyl-*N*-[3-oxo-(*E,E*)-4,6-octadienoyl]glycinate (**55**), but cyclization with sodium methoxide gave the desired 1-methyl-3-sorbyl-2,4-pyrrolidione (**41**)[14] in less than 1% yield (Figure 4).

As alternative synthons for the N-1, C-4, and C-5 positions of the tetramic acid unit *N*-benzylaminoacetonitrile and *N*-

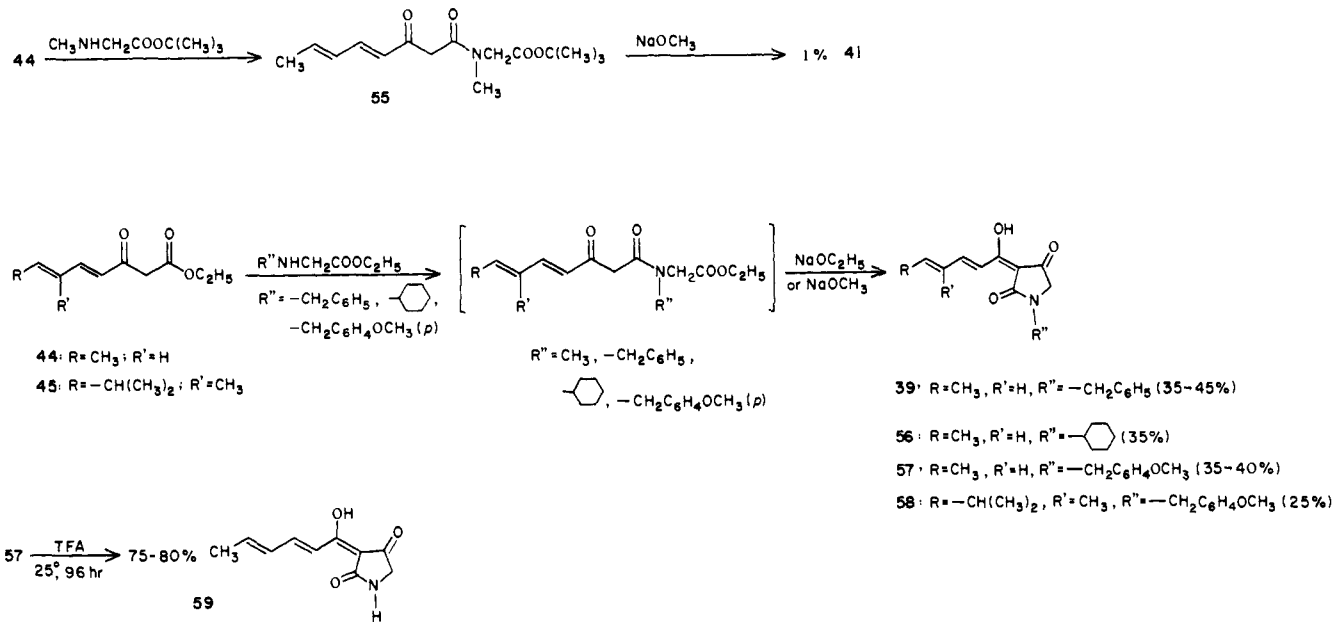


Figure 4. Preparation of 3-dienoyl-2,4-pyrrolidiones (**39, 41, 56–58**) by cyclization of *N*-dienoylacetyl-*N*-alkylglycine esters.

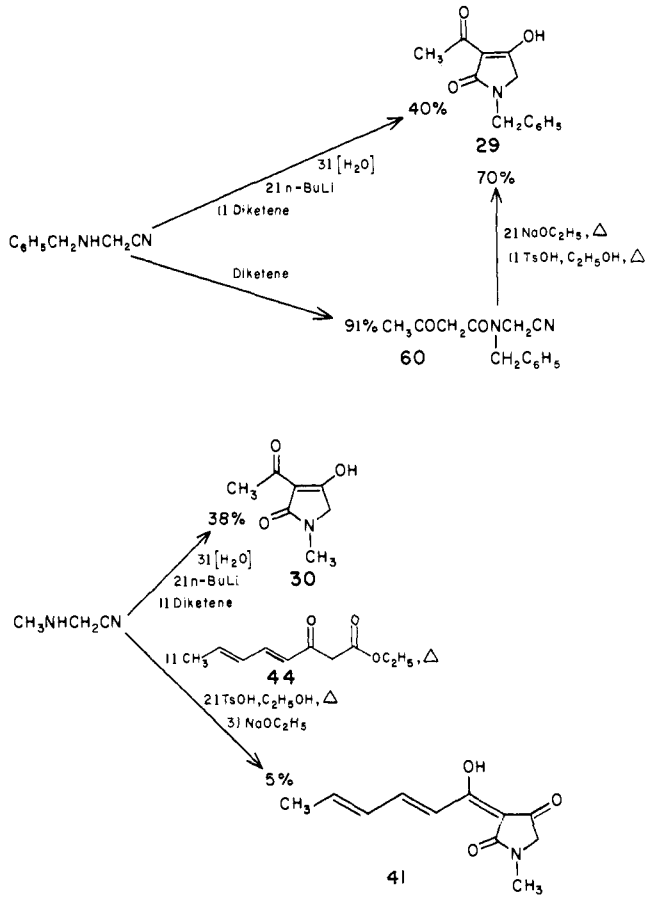


Figure 5. Preparation of 3-acyl-2,4-pyrrolidiones (**29, 30, 41**) from α-(alkylamino)acetonitriles.

methylaminoacetonitrile were condensed with diketene and the corresponding *N*-alkyl-α-(acetoacetamido)acetonitriles were cyclized in ca. 40% yields to the 3-acetyl tetramic acids **29** and **30**[14] by heating the lithium enolates in refluxing glyme for 48 h (Figure 5).

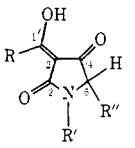
An alternative route from the α-(acetoacetamido)acetonitriles involved conversion of the nitriles to ethyl esters with 1 equiv of *p*-toluenesulfonic acid monohydrate in refluxing alcohol[23] and cyclization to the tetramate. Under these conditions *N*-benzyl-α-(acetoacetamido)acetonitrile (**60**) gave **29**[14] in 70% yield based on starting nitrile (Figure 5). By the same procedure the crude *N*-alkyldienoylacetamidoacetonitrile from condensation of *N*-methylaminoacetonitrile with ethyl 3-oxo-(*E,E*)-4,6-octadienoate (**44**) gave 1-methyl-3-sorbyl-2,4-pyrrolidione (**41**)[14] in 5% overall yield from *N*-methylaminoacetonitrile (Figure 5).

Spectroscopic Properties of Model 3-Dienoyl Tetramic Acids. The ultraviolet behavior of the 3-dienoyl tetramic acids was compared to that of streptolydigin (**1**) and tirandamycin (**2**). Both synthetic and natural compounds showed the same unusual behavior on changing from acidic to basic solution (Table II), involving a hypsochromic shift of the maximum at longest wavelength (near 350 nm) and a bathochromic shift of the maximum at shortest wavelength (near 230 nm). The 3-acetyl tetramic acids are also unusual, in that their maxima at longest wavelength do not shift in position in base but increase in intensity. This ultraviolet behavior is characteristic for the acetyl tetramic acids, and contrasts with that of other β-triketones (e.g., 2-acetyldimedone and triacetylmethane)[3] as well as the dienoylacetyl esters of the present study, which show a bathochromic shift in base of the maxima at longest wavelength.

The ^{13}C NMR spectra of the 3-acetyl tetramic acids (**11, 21**) and the 3-dienoyl tetramic acids (**39, 56, 59**) show that chemical shifts for certain carbon nuclei are sufficiently invariant to allow assignments to be made with confidence (Table III). Some carbon resonances were assigned on the basis of general principles or the multiplicity observed in off-resonance decoupled spectra. This, for example, was the case with C-3 and C-5, which appear at 101.7 and 51.0 ppm in the spectrum of the simplest acyl tetramic acid, **21** (singlet and triplet, respectively, in the off-resonance spectrum), and at similar positions (100–102, 51–55 ppm) in the spectra of **11, 39, 56,** and **59** (except **11,** where C-5 is at 63.8 ppm). The amide carbon (C-2) of **21** must be that at 174.5 ppm and C-2 for the other compounds is in the range 173–178 ppm. Analogy for C-2 is found in caprolactam, where the carbonyl carbon appears at 178.6 ppm.[24] Conjugation to an unsaturated system should result in a ca. 5 ppm upfield shift, as observed for C-1 of 2-cyclopentenone (208.1 ppm) vs. C-1 of cyclopentanone (213.9 ppm).

The acetyl methyl appears at 19.8 ppm for **21** and 2′- and

Table III. ^{13}C NMR Spectral Data for 3-Acetyl and 3-Dienoyl Tetramic Acids



Carbon	Chemical shift, ppm[a]				
	3-Acetyl (R = CH_3)		3-Dienoyl (R = $CH_3CH{=}CHCH{=}CH$-)		
	21[b]	**11**	**39**	**56**	**59**[c]
C-2	174.5	173.0	173.4*	173.8*	177.5
C-3	101.7	101.8	100.4	101.2	101.8
C-4	193.1	194.0	190.9	191.7	182.9
C-5	51.0	63.8	54.9	51.6	53.4
C-1′	184.6	184.3	173.6*	173.2*	177.5
C-2′	19.8	19.6	119.3	119.7	119.2
C-3′			144.8	144.6	155.6
C-4′			130.9	131.2	133.1
C-5′			142.0	141.8	152.4
C-6′			19.0	19.0,	19.9
R′		26.5*[d]	45.4, 135.3, 126.7, 127.9, 128.0[e]	49.4, 30.7, 25.4[f]	
R″		27.0*, 36.5, 169.3[d]			

[a] Deuteriochloroform solution and R′ = R″ = H, except as noted. Asterisks indicate interchangeable assignments. [b] Dimethyl-d_6 sulfoxide solution. [c] Trifluoroacetic acid solution. [d] R′ = CH_3; R″ = $CH_2CONHCH_3$. [e] R′ = $C_6H_5CH_2$. [f] R′ = cyclohexyl.

6′-methyl carbons in the range 19.0–19.9 ppm for the other compounds. In the dienoyl side chain the β olefinic carbon should be the furthest downfield followed by the δ, γ, and α carbons on the basis of the resonance interactions of the dienoyl system, which place the lowest electron density on the β carbon, followed by the δ carbon. Confirmation of these olefinic carbon assignments was achieved by specific proton decoupling studies. The enolic C-1′ carbon is similar to C-4 in the enolic form of acetylacetone, which appears at 190.0 ppm.[25]

The most difficult carbons of **21** to assign are C-4 and C-1′, which give the signals at 184.6 and 193.1 ppm. The latter signal does not shift much (1–2 ppm) in the 3-dienoyl tetramic acids (except **59**, where the trifluoroacetic acid solvent is presumably responsible), but the former signal moves upfield by over 10 ppm. Thus, the signal at 193.1 ppm can be assigned to C-4 and that at 184.6 ppm to C-1′.

Experimental Section

General. Melting points, determined on a Kofler hot stage, are uncorrected, as are boiling points. Infrared (IR) spectra were determined on a Beckman spectrophotometer, Model IR-12, and ultraviolet (UV) spectra on a Beckman spectrophotometer, Model DB, or on a Coleman-Hitachi spectrophotometer. Proton magnetic resonance (^1H NMR) spectra were determined by Mr. R. Thrift and associates on Varian A-60, HA-100, and HR-220 spectrometers. Carbon magnetic resonance (^{13}C NMR) spectra were determined on a Varian XL-100 spectrometer. Chemical shifts are reported in parts per million from Me_4Si as internal standard. Low-resolution mass spectra were obtained by Mr. J. Wrona on a Varian MAT CH-5 DF mass spectrometer, and high-resolution data by Mr. J. C. Cook, Jr., and associates on a Varian MAT 731 mass spectrometer. Microanalyses were determined by Mr. J. Nemeth and associates.

The "usual" workup consisted of diluting the reaction mixture with water, extracting several times with the appropriate water-immiscible solvent, combining the organic extracts, drying the extracts over a filter cone of anhydrous magnesium sulfate or sodium sulfate, and concentrating in vacuo.

Diethyl DL-*N*-Methylaspartate (6). Methylamine (62.3 g, 2.0 mol) was bubbled into a cooled solution of 344.4 g (2.0 mol) of freshly distilled diethyl maleate (5–10 °C). The solution was heated at reflux for 1 h, then concentrated in vacuo. The residue was distilled to give 344.0 g (85%) of amino ester: bp 87–89 °C (1 Torr); IR (film) 3365 and 1745 cm^{-1}; ^1H NMR ($CDCl_3$) 1.24 and 1.26 (t and t, 6 H, CH_3CH_2O), 1.89 (s, 1 H, NH), 2.44 (s, 3 H, CH_3N), 2.65 (m, 2 H, $CHCH_2$), 3.56 (dd, 1 H, CHN), and 4.15 and 4.21 ppm (q and q, 4 H, OCH_2).

Anal. Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.17; H, 8.50; N, 6.85.

3-Acetyl-1-methyl-2,4-pyrrolidione-5-(ethyl acetate) (7). Freshly distilled diketene (124.7 g, 1.48 mol) was added dropwise at 0–5 °C to a solution of 301.0 g (1.48 mol) of freshly distilled **6** in 500 mL of dry benzene. The solution was stirred at 25 °C for 2 h, then added dropwise to an ethanolic sodium ethoxide solution (34.5 g of sodium metal in 400 mL of anhydrous ethanol). The mixture was stirred at 25 °C for 14 h and the ivory-colored tetramate salt was collected, dried, and dissolved in 3 N hydrochloric acid. Extraction with ether and workup of the organic extracts gave 328.2 g (92%) of light yellow oil (**7**) which gave an intense brown coloration with ferric chloride spray reagent: ^1H NMR ($CDCl_3$, 100 MHz) 1.21 (t, 3 H, CH_3CH_2), 2.36 (s, 3 H, CH_3CO), 2.80 (m, 2 H, $CHCH_2$), 2.95 (s, 3 H, CH_3N), 4.00 (m, 1 H, CHN), and 4.10 ppm (q, 2 H, OCH_2).

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.76; H, 6.26; N, 5.80. Found: C, 54.69; H, 6.25; N, 5.82.

1-Methyl-3-(1-methylaminoethylidene)-2,4-pyrrolidione-5-(methyl acetate) (12). A solution of 2.41 g (10 mmol) of **7** and 20 mL (20 mmol) of 1 N methanolic methylamine was heated at reflux for 3 h and concentrated in vacuo. The residue was recrystallized from benzene–petroleum ether to afford 1.90 g (80%) of enamine (**12**): mp 96–96.5 °C; IR ($CHCl_3$) 1730 and 1600 cm^{-1}; ^1H NMR ($CDCl_3$) 2.53 (s, 3 H, $CH_3C{=}$), 2.65 (m, 2 H, CH_2), 2.91 (s, 3 H, NCH_3), 3.06 (d, 3 H, CH_3NH), 3.70 (s, 3 H, OCH_3), and 3.94 ppm (m, 1 H, CH).

Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.89; H, 6.75; N, 11.60.

1-Methyl-3-(1-methylaminoethylidene)-2,4-pyrrolidione-5-(*N*-methylacetamide) (8). A solution of 195.0 g (1.362 mol) of **7** and 250 mL of liquefied methylamine in 450 mL of absolute ethanol was gradually heated to reflux under a dry ice condenser during 5 h, then for 2 h under a water-cooled condenser. The solvent was removed in vacuo and the residue was recrystallized from ethyl acetate to give 260.4 g (80%) of white, amorphous product (**8**): mp 172–174 °C; IR (KBr) 3450, 1686, and 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) 2.50 (s, 3 H, $CH_3C{=}$), 2.53 (m, 2 H, CH_2CO), 2.78 (d, 3 H, $CONHCH_3$), 2.88 (s, 3 H, CH_3NCH), 3.04–3.07 (two doublets, 3 H, $CH_3NHC{=}$), 3.95 (m, 1 H, $CHCH_2$), and 7.10 ppm (bd, 2 H, $NHCH_3$).

Anal. Calcd for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16; N, 17.56; mol wt, 239.1270. Found: C, 55.48; H, 7.16; N, 17.67; mol wt, 239.1266 (HRMS).

3-Acetyl-1-methyl-2,4-pyrrolidione-5-(acetic acid) (13). A mixture of 2.41 g (10 mmol) of **7**, 1.0 g (25 mmol) of sodium hydroxide, and 30 mL of water was heated at reflux for 4 h and concentrated in vacuo. The residue was acidified and extracted with chloroform. The organic extracts were worked up to give, after crystallization from benzene, 2.10 g (98%) of pink prisms (**13**): mp 106–107 °C; IR (KBr) 3420, 1710, and 1625 cm^{-1}; ^1H NMR (TFA) 2.62 (s, 3 H, CH_3CO), 3.16 (s, 3 H, CH_3N), 3.19 (d, 2 H, CH_2CH), and 4.41 ppm (t, 1 H, $CHCH_2$).

Anal. Calcd for $C_9H_{11}NO_5$: C, 50.71; H, 5.20; N, 6.57. Found: C, 50.98; H, 5.26; N, 6.31.

1-Methyl-2,4-pyrrolidione-5-(*N*-methylacetamide) (5). A solution of 35.0 g (140 mmol) of **8** in 1 L of 0.2 N hydrochloric acid was heated at reflux for 5 h, then allowed to stand overnight. Concentration in vacuo gave a noncrystalline residue which was chromatographed (silica gel, gradient elution, 2% → 5% MeOH in $CHCl_3$) to give an off-white solid. Recrystallization from methanol–ethyl acetate gave 10.0 g (38%) of white product (**5**): mp 161–162 °C; IR (KBr) 1720 and 1670 cm^{-1}; ^1H NMR (CD_3SOCD_3, 100 MHz) 2.51 (m, 2 H, CH_2CH), 2.65 and 2.70 (s and s, 6 H, NCH_3), 3.87 (m, 1 H, $CHCH_2$), and 6.50 ppm (s, 1 H, HC=).

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.28; H, 6.34; N, 15.29.

1-Methyl-2,4-pyrrolidione-5-(*N*-methylacetamide) Thallium(I) Salt (14). A mixture of 6.15 g (33.3 mmol) of **5** and 8.35 g (35 mmol) of thallous ethoxide (Aldrich Co.) in 100 mL of dry dimethylformamide was stirred overnight at 25 °C. The off-white solid was collected, washed with dimethylformamide and ether, and stored overnight at 1.0 mm in a desiccator to give 12.81 g (98%) of product (**14**): mp 219–220 °C; IR (KBr) 3311, 1665, and 1576 cm^{-1}.

Anal. Calcd for $C_8H_{11}N_2O_3Tl$: C, 24.79; H, 2.86; N, 7.23. Found: C, 25.07; H, 2.88; N, 7.01.

3-Acetyl-1-methyl-2,4-pyrrolidione-5-(*N*-methylacetamide) (11). A. From Acylation of Enolate 14. A mixture (10 drops) of acetyl fluoride (K and K Laboratory) and 270 mg (0.697 mmol) of **14** in 10 mL of dry dimethylformamide was stirred at 25 °C for 5 h. Thallium fluoride was filtered and washed with dimethylformamide and the solvent was removed in vacuo, leaving a yellow oil which was taken up in chloroform and extracted with 5% sodium hydroxide. The neutral organic phase yielded 23 mg of the starting pyrrolidione **5**, while acidification of the alkaline aqueous phase followed by chloroform extraction gave 97 mg of product (**11**), giving an intense brown coloration with ferric chloride reagent. Recrystallization of the product from ethyl acetate–hexane gave 72 mg (57%) of fine, white needles: mp 144–147 °C; IR ($CHCl_3$) 3320 and 1710–1630 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) 2.42 (s, 3 H, CH_3CO), 2.55 (m, 2 H, CH_2CH), 2.80 (d, 3 H, $CHNH$–), 2.98 (s, 3 H, CH_3N), 4.11 (m, 1 H, $CHCH_2$), 6.20 (bs, 1 H, NH), and 13.05 ppm (s, 1 H, OH).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.95; H, 6.16; N, 12.43.

B. From Alkaline Hydrolysis of 8. A solution of 532 mg (2.23 mmol) of **8** and 50 mL of 0.3% methanolic sodium hydroxide was heated at reflux for 36 h. The solvent was removed in vacuo and the residue was acidified and extracted with chloroform. The chloroform extracts were worked up and the product (**11**) was recrystallized from ethyl acetate–hexane to afford 235 mg (46%) of white crystals, mp 146–147 °C, whose spectral and physical properties were identical with those of a sample prepared by procedure A.

Crotonyl Fluoride. A procedure modified from that of Seel and Langer[16] was utilized. A mixture of 31.3 g (300 mmol) of freshly distilled crotonyl chloride and 40.0 g (320 mmol) of potassium fluorosulfinate was heated at 105–110 °C for 2.5 h. The temperature of the flask was lowered to 60 °C, the condenser was replaced with a distillation head, and the product was distilled to afford 15.0 g (57%) of crotonyl fluoride, bp 78–81 °C (lit.[16] 81–82 °C).

Sorbyl Fluoride. A mixture of 33.7 g (300 mmol) of sorbic acid, 25.0 g (310 mmol) of dry pyridine, 13.7 g (100 mmol) of cyanuric fluoride (Aldrich Co.), and 300 mL of dry acetonitrile was kept at 35–40 °C for 4 h. The greenish-yellow precipitate was filtered and the filtrate was partitioned between cold 1 N hydrochloric acid and ether. The ethereal extracts were washed with cold sodium bicarbonate and saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Distillation gave 21 g (61%) of sorbyl fluoride, bp 61–62 °C (30 Torr) [lit.[16] 40–41 °C (12 Torr)].

Sorbyl Chloride. A mixture of 33.7 g (300 mmol) of sorbic acid, 50 mL of thionyl chloride, and 100 mL of dry benzene was heated at reflux for 1 h. Excess solvent was removed in vacuo and the residue was distilled to yield 35.3 g (90%) of sorbyl chloride, bp 39–40 °C (1 Torr) [lit.[16] 80–84 °C (20 Torr)].

Acylation of Enolate 14 with Sorbyl Fluoride. A mixture of 3.87 g (10 mmol) of **14**, 2.20 g (20 mmol) of sorbyl fluoride, and 40 mL of dry dimethylformamide was heated at 85 °C for 2 h. The thallium salts were filtered and washed with solvent, and the filtrate was concentrated in vacuo. The residue was chromatographed (Florisil gradient elution, 0–30% MeOH in $CHCl_3$) to give two fractions. The initial fraction eluted gave 1.20 g (43%) of the N-acylated product, 1-methyl-2,4-pyrrolidione-5-(*N*-methyl-*N*-sorbylacetamide) (**16**) as a faint yellowish-orange oil which gradually solidified: IR ($CHCl_3$) 1700, 1645, and 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) 1.86 (m, 3 H, CH_3CH=), 2.39 and 2.90 (bd and m, 2 H, CH_2CH), 2.76 (s, 3 H, CH_3N), 2.83 (s, 3 H, CH_3N), 2.90–3.05 (m, 2 H, $COCH_2CO$), 4.38 (dd, 1 H, $CHCH_2$), 5.78 (d, 1 H, α =CH), 6.20–6.40 (m, 2 H, γ and δ =CH), and 7.28 ppm (m, 1 H, β =CH).

Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.06. Found: C, 60.35; H, 6.34; N, 10.00.

The second fraction, which gave a positive ferric chloride coloration, was further purified by chromatography (Sephadex LH-20, MeOH) to give orange 1-methyl-3-sorbyl-2,4-pyrrolidione-5-(*N*-methylacetamide) (**15**): mp 171–174 °C; ^1H NMR, see Table I.

Anal. Calcd for $C_{14}H_{18}N_2O_4$: mol wt, 278. Found: mol wt, 278 (mass spectrum).

1-Methyl-4-sorbyloxy-3-pyrrolin-2-one-5-(*N*-methylacetamide) (17). A mixture of 1.95 g (5 mmol) of **14**, 650 mg (5 mmol) of distilled sorbyl chloride, and 25 mL of dry dimethylformamide was stirred at 25 °C for 12 h. Thallium chloride was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed (Bio-Sil A, 2% MeOH in $CHCl_3$) to give 454 mg (32%) of pale orange product (**17**): mp 136–138 °C; IR ($CHCl_3$) 3574, 1737, 1715, 1682, 1640, and 1134 cm^{-1}; ^1H NMR, see Table I. The analytical sample was prepared by preparative TLC (silica gel GF_{254}, 2% MeOH in $CHCl_3$).

Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.06; mol wt, 278.1267. Found: C, 60.22; H, 6.30; N, 9.70; mol wt, 278.1270 (HRMS).

4-(4,6-Dimethyl-(*E,E*)-2,4-heptadienoyloxy)-1-methyl-3-pyrrolin-2-one-5-(*N*-methylacetamide) (19). A solution of 445 mg (2.42 mmol) of **5** in 15 mL of distilled dry dimethylformamide was cooled to 0 °C, and 146 mg of sodium methoxide was added, followed after 30 min by 240 mg (2.42 mmol) of freshly distilled 4,6-dimethyl-(*E,E*)-2,4-heptadienoyl chloride (**18**; cf. below for preparation). The mixture was stirred at 0 °C for 1 h, then concentrated in vacuo (0.1 mm). The residue was acidified and the product was extracted into chloroform and worked up to afford an orange oil, which was chromatographed (Florisil, 5% MeOH in $CHCl_3$) to give 150 mg (19%) of O-acylation product **19** as an orange oil: IR ($CHCl_3$) 1735, 1670, and 1650 cm^{-1}; ^1H NMR, see Table I.

Anal. Calcd for $C_{17}H_{24}N_2O_4$: mol wt, 320.4. Found: mol wt, 320 (mass spectrum).

3-Acetyl-2,4-pyrrolidione (21). The procedure of Lacey,[13a] employing 34.9 g (250 mmol) of ethyl glycinate hydrochloride, 21.1 g (250 mmol) of distilled diketene, and 125 mL of 2 N ethanolic sodium ethoxide, gave 25.5 g (50%) of acetyl tetramate **21**, mp 155 °C (lit.[13a] 155 °C).

3-Acetyl-1-benzyl-2,4-pyrrolidione (29). A solution of 19.32 g (100 mmol) of ethyl *N*-benzylglycinate[26] and 8.4 g (100 mmol) of freshly distilled diketene in 200 mL of benzene stood for 2 h, and 125 mL of 1 N ethanolic sodium ethoxide was added. The mixture was stirred overnight, acidified, and extracted with chloroform. The usual workup gave an oil, which crystallized from benzene–petroleum ether to afford 20.8 g (90%) of acyltetramic acid **29**: mp 69–70 °C; IR ($CHCl_3$) 1710, 1645, 1622, and 1250 cm^{-1}; ^1H NMR ($CDCl_3$) 2.37 and 2.48 (s, 3 H, CH_3CO), 3.54 and 3.62 (s, 2 H, NCH_2), 4.53 (s, 2 H, $C_6H_5CH_2$), and 7.21 ppm (s, 5 H, C_6H_5).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06; mol wt, 231.0895. Found: C, 67.52; H, 5.74; N, 6.06; mol wt, 231.0894 (HRMS).

3-Acetyl-1-methyl-2,4-pyrrolidione (30). The procedure of Lacey,[13a] utilizing 46.8 g (400 mmol) of ethyl sarcosinate **28**, 33.6 g (400 mmol) of distilled diketene, and 200 mL of 2 N ethanolic sodium ethoxide, gave 58.0 g (79%) of tetramate **30**, mp 48–50 °C (lit.[13a] 46–49 °C).

Acidic Hydrolysis of 3-Acetyl-2,4-pyrrolidione (21). A mixture of 1.41 g (10 mmol) of **21** and 100 mL of 0.2 N hydrochloric acid was

heated at reflux for 5 h, then concentrated in vacuo to give the ivory-colored dimer (**22**), mp >300 °C (lit.[18] >300 °C). This material gave an intense purple coloration with ferric chloride reagent.

Acidic Hydrolysis of 3-Acetyl-1-benzyl-2,4-pyrrolidione (29). A mixture of 1.16 g (5 mmol) of **29** and 100 mL of 0.2 N hydrochloric acid was heated at reflux for 5 h and concentrated in vacuo to give the solid yellow dimer (**31a**), mp 205–206 °C, insoluble in acetonitrile, chloroform, and ethanol: IR (KBr) 3435, 1685, 1450, and 705 cm^{-1}.

Anal. Calcd for $C_{22}H_{20}N_2O_3 \cdot {}^1/_2H_2O$: C, 71.53; H, 5.73; N, 7.58; mol wt, 360.1473. Found: C, 71.45; H, 5.56; N, 7.36; mol wt, 360.1465 (HRMS).

Acidic Hydrolysis of 3-Acetyl-1-methyl-2,4-pyrrolidione (30). A mixture of 2.1 g of **30** and 50 mL of 0.05 N hydrochloric acid was heated at reflux for 1 h, cooled, and filtered. The precipitated dimer (**31b**) weighed 150 mg after crystallization from methanol, mp >250 °C.

Anal. Calcd for $C_{10}H_{12}N_2O_3 \cdot 0.25H_2O$: C, 56.49; H, 5.91; N, 13.16; mol wt, 208. Found: C, 56.63; H, 5.83; N, 12.90; mol wt, 208 (mass spectrum).

3-Carbethoxy-2,4-pyrrolidione (23). A solution of 30.9 g (300 mmol) of ethyl glycinate, 39.7 g (300 mmol) of monoethyl malonate, and 350 mL of methylene chloride was cooled to 0–5 °C and 38.0 g (305 mmol) of *N,N'*-diisopropylcarbodiimide was added dropwise. After 12 h, the precipitate was collected and the filtrate was concentrated in vacuo to give the yellow, oily amide, which was dissolved in 400 mL of benzene and stirred at reflux with 155 mL of 2.0 N ethanolic sodium ethoxide for 1 h. Solvent was removed in vacuo and the tan salt was dissolved in a minimal amount of cold water and acidified with cold hydrochloric acid. After cooling at 0 °C for 12 h, the precipitate was collected and air dried to afford 17.0 g (53%) of **23**, which when heated at a fast rate showed transient melting at ca. 140 °C followed by resolidification and no further melting to 300 °C, as reported[18] earlier: IR (KBr) 3250–3075, 1715, 1665 and 1632 cm^{-1}.

1-Benzyl-3-carbethoxy-2,4-pyrrolidione (32). A solution of 22.2 g (115 mmol) of ethyl *N*-benzylglycinate,[26] 15.25 g (115 mmol) of monoethyl malonate, and 250 mL of dry methylene chloride was cooled to 0–5 °C and 14.7 g (116 mmol) of *N,N'*-diisopropylcarbodiimide was added dropwise. The mixture stood at 25 °C for 4 h, the white precipitate was filtered, and the filtrate was concentrated in vacuo to give 33.6 g (95%) of light yellow amide. A solution of the amide in 250 mL of dry benzene and 120 mL (120 mmol) of 1 N ethanolic sodium ethoxide solution was then heated at reflux for 1 h, water (175 mL) was added, and the layers were separated. The aqueous phase was acidified and extracted with chloroform; workup of the chloroform extracts gave an amorphous solid. Quick recrystallization from benzene–cyclohexane gave 27.1 g (90%) of pale crystalline product (**32**): mp 148.5–150 °C; IR (KBr) 1700, 1655, and 1634 cm^{-1}; ^1H NMR ($CDCl_3$) 1.38 (t, 3 H, CH_3CH_2), 3.81 (s, 2 H, NCH_2), 4.37 (q, 2 H, OCH_2), 4.56 (s, 2 H, $C_6H_5CH_2$–), 7.24 (s, 5 H, C_6H_5), and 11.01 ppm (s, 1 H, OH).

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36; mol wt, 261.1001. Found: C, 64.54; H, 5.76; N, 5.25; mol wt, 261.1001 (HRMS).

3-Carbethoxy-1-methyl-2,4-pyrrolidione (33). *N,N'*-Diisopropylcarbodiimide (41.7 g, 330 mmol) was added dropwise to a solution of 43.5 g (370 mmol) of ethyl sarcosinate,[27] 43.8 g (330 mmol) of monoethyl malonate, and 250 mL of dry methylene chloride. After 3 h, the precipitate was filtered and washed with methylene chloride, and the filtrate was concentrated in vacuo to give the crude β-keto amide, which was dissolved in 200 mL of dry benzene, treated with 175 mL (350 mmol) of 2 N ethanolic sodium ethoxide, and stirred at 25 °C for 18 h. The reaction mixture was diluted with 200 mL of water, the layers were separated, and the aqueous phase was cooled and acidified to give a white precipitate (**33**), which was collected, air dried, and kept overnight in a desiccator over potassium hydroxide pellets, yield 42.0 g (70%), mp 188–190 °C (lit.[18] 190–192 °C).

2.4-Pyrrolidione Thallium(I) Salt (24). A solution of 4.28 g (25 mmol) of **23** in 150 mL of nitromethane refluxed for 1 h, then was concentrated in vacuo to give 1.25 g (50%) of the crude pyrrolidione **20.** The pyrrolidione was dissolved in 100 mL of dry benzene and treated with 3.74 g (13 mmol) of thallium(I) ethoxide; after 30 min, a tan precipitate was observed. The mixture was allowed to stand overnight, then the precipitate was collected, washed with ether, and stored in a desiccator overnight. The material turned dark brown on standing for 15 min. A freshly prepared sample was observed to decompose at 35 °C. Attempts to obtain satisfactory elemental analyses were unsuccessful.

1-Benzyl-2,4-pyrrolidione (27). Finely pulverized **32** (2.61 g, 10 mmol) was added to 100 mL of boiling water and stirred rapidly. After 5 min, the mixture was cooled in an ice bath and extracted with chloroform. The organic extracts were washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 1.75 g (93%) of yellow, oily product (**27**). Normally the crude pyrrolidione was converted to the thallium enolate (cf. **25** below) without additional purification. The analytical sample obtained by chromatography (silica gel, $CHCl_3$) was a yellow oil which solidified under vacuum: mp 64–66 °C; IR (film) 1779, 1700, and 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) 3.05 (s, 2 H, $COCH_2$), 3.72 (t, 2 H, $J \leq 1$ Hz, NCH_2), 4.62 (s, 2 H, $C_6H_5CH_2$–), and 7.31 ppm (s, 5 H, C_6H_5).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40; mol wt, 189.0789. Found: C, 70.00; H, 5.75; N, 7.28; mol wt, 189.0786 (HRMS).

When a sample of **27** sat at 25 °C for 4 days it gave the yellow, amorphous dimer (**31a**), mp 205–206 °C, This material (**31a**) was identical in all physical and spectroscopic properties with the dimer obtained when 3-acetyl-1-benzyl-2,4-pyrrolidione (**29**) was hydrolyzed in acid (cf. above).

1-Benzyl-2,4-pyrrolidione Thallium(I) Salt (25). A mixture of 5.50 g (29 mmol) of freshly prepared **27** and 7.70 g (32 mmol) of thallous ethoxide in 50 mL of dry dimethylformamide was stirred at 25 °C for 4 h, anhydrous ether (100 mL) was added, and the light tan precipitate was stirred overnight. The salt was collected and washed with ether: 10.9 g (91%); mp 109–111 °C; IR (KBr) 1640, 1576, and 1455 cm^{-1}. The thallium(I) salt (**25**) turned to a brown gum with other solvents.

Anal. Calcd for $C_{11}H_{10}NO_2Tl$: C, 33.06; H, 2.57; N, 3.57. Found: C, 33.19; H, 2.44; N, 3.34.

1-Methyl-2,4-pyrrolidione (28). The procedure of Mulholland et al.[18] was utilized. Finely pulverized **33** (1.85 g, 10 mmol) was added to boiling water and stirred vigorously for 6 min, then cooled and concentrated in vacuo at 30–35 °C (1 Torr) to a yellow oil which was dissolved in acetonitrile; the solution was filtered and concentrated in vacuo. Sublimation at 40 °C (1 Torr) gave 505 mg (43%) of hygroscopic solid, mp 49–50 °C (lit.[18] mp 48–51 °C).

1-Methyl-2,4-pyrrolidione Thallium(I) Salt (26). When a solution of 2.55 g (22 mmol) of freshly prepared **28** in 50 mL of dimethylformamide was treated with 5.49 g (22 mmol) of thallous ethoxide, the orange color was immediately discharged to give a light tan precipitate. After 12 h, the salt was collected, washed with dimethylformamide and ether, and stored overnight at 58 °C (1 Torr): yield 5.95 g (94%); mp 179–180 °C; IR (KBr) 1660, 1636, 1585, 1146, and 810 cm^{-1}.

Anal. Calcd for $C_5H_6NO_2Tl$: C, 18.98; H, 1.91; N, 4.42. Found: C, 18.76; H, 1.99; N, 3.91.

Acylation of Thallium Enolate 25 with Crotonyl Fluoride. A mixture of 1.00 g (2.5 mmol) of **25,** 0.45 g (5 mmol) of crotonyl fluoride, and 25 mL of dry dimethylformamide was stirred at 45 °C for 10 h. The thallium salts were filtered and the filtrate was concentrated in vacuo. The residue was partitioned between chloroform and 5% sodium hydroxide and the organic phase (neutral) was concentrated and chromatographed (Bio-Sil A, $CHCl_3$) to afford 136 mg (20%) of low-melting 1-benzyl-4-crotonyloxy-3-pyrrolin-2-one (**34**), which gave a negative ferric chloride test: mp 50–52 °C; IR ($CHCl_3$) 1753, 1685, and 1623 cm^{-1}; ^1H NMR, see Table I.

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44; mol wt, 257.1051. Found: C, 69.82; H, 5.95; N, 5.24; mol wt, 257.1041 (HRMS).

Acylation of Thallium Enolate 25 with Sorbyl Fluoride. A mixture of 1.31 g (3.3 mmol) of **25,** 0.50 g (4.2 mmol) of sorbyl fluoride, and 30 mL of dry dimethylformamide was stirred at 25 °C for 4 h. The thallium salts were filtered and the filtrate was concentrated in vacuo. The residue was chromatographed (silica gel, C_6H_6–$CHCl_3$, 9:1) to give 300 mg (31%) of 1-benzyl-4-sorbyloxy-3-pyrrolin-2-one (**35**), which gave a negative ferric chloride test: mp 76–78 °C; IR ($CHCl_3$) 1750, 1685, 1650, 1615, 1324, 1170–1240, and 1111 cm^{-1}; ^1H NMR, see Table I.

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94; mol wt, 283.1208. Found: C, 72.13; H, 6.02; N, 5.05; mol wt, 283.1206 (HRMS).

Acylation of Thallium Enolate 26 with Crotonyl Fluoride. A mixture

of 3.25 g (10 mmol) of **26**, 0.90 g (10 mmol) of distilled crotonyl fluoride, and 30 mL of dry dimethylformamide was stirred at 25 °C for 8 h, the salts were filtered, and the filtrate was concentrated in vacuo. The residue was partitioned between chloroform and 5% sodium hydroxide and the organic phase (neutral) was concentrated and chromatographed (Bio-Sil A, $CHCl_3$) to afford 260 mg (15%) of a tan solid (**36**) which gave a negative ferric chloride response: mp 72 °C; IR ($CHCl_3$) 1754, 1685, and 1628 cm^{-1}; ^1H NMR, see Table I.

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73; mol wt, 181.0729. Found: C, 59.47; H, 5.91; N, 7.85; mol wt, 181.0736 (HRMS).

The alkaline extract was acidified and extracted with chloroform, affording an inseparable 1:2 mixture (125 mg) of 3-crotonyl-1-methyl-2,4-pyrrolidione (**40**) and crotonic acid. The ^1H NMR showed distinct resonances for the *C*-acyl product (cf. Table I).

Acylation of Thallium Enolate 26 with Sorbyl Fluoride. A mixture of 3.21 g (10 mmol) of **26**, 1.25 g (11 mmol) of distilled sorbyl fluoride, and 75 mL of dry dimethylformamide was stirred at 25 °C for 3 h. The thallium salts were filtered and washed with solvent, and the filtrate was concentrated in vacuo. The residue was partitioned between chloroform and 0.1 N sodium hydroxide and the neutral material was chromatographed (Bio-Sil A, $CHCl_3$) to give 540 mg (26%) of 1-methyl-4-sorbyloxy-3-pyrrolin-2-one (**37**), mp 85–89 °C. Additional purification by preparative TLC on silica gel, employing 2% methanol in chloroform, gave a yellowish-orange, waxy solid: IR ($CHCl_3$) 1751, 1688, 1651, 1618, 1335, 1245, 1185, and 1118 cm^{-1}; ^1H NMR, see Table I.

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76; mol wt, 207.0895. Found: C, 63.51; H, 6.46; N, 6.48; mol wt, 207.0902 (HRMS).

The alkaline aqueous extract was acidified and extracted with chloroform. The organic extracts were concentrated in vacuo and the residue was chromatographed (Bio-Sil A, $CHCl_3$) to give 120 mg (6%) of lemon yellow product (**41**), mp 85–90 °C, which gave an intense brownish-orange ferric chloride response. Crystallization from ether–petroleum ether gave 100 mg of the desired acyl tetramate (**41**): IR (CCl_4) 1695, 1625, 1565, and 1005 cm^{-1}; ^1H NMR, see Table I.

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76; mol wt, 207.0895. Found: C, 63.38; H, 6.23; N, 6.63; mol wt, 207.0900 (HRMS).

Ethyl 3-Oxo-(*E,E*)-4,6-octadienoate (44). A solution of 13.2 g (100 mmol) of monoethyl malonate was added to a slurry of 25.0 g (210 mmol) of magnesium ethoxide in 250 mL of dry tetrahydrofuran. The resulting yellow solution was heated at reflux for 6 h and 13.1 g (100 mmol) of distilled sorbyl chloride was added. The mixture was heated at reflux for 6 h and hydrochloric acid (2 N) was added dropwise until gas evolution had ceased. The product was extracted into ether and worked up to give, after distillation, 11.0 g (60%) of yellow ester (**44**): bp 95–100 °C (1.5 Torr); IR (film) 1755, 1662, 1274, 1051, and 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) (keto form) 1.24 (t, CH_3CH_2O), 1.89 (m, CH_3CH=), 3.56 (s, $COCH_2CO$), 4.17 (q, CH_2O), 6.12 (d, α =CH), 6.18 (m, γ and δ =CH), and 7.23 ppm (m, β =CH); ^1H NMR (enol form) 1.26 (t, CH_3), 1.89 (m, CH_3CH=), 4.18 (q, OCH_2), 4.99 (s, HC=COH), 5.78 (d, α =CH), 6.18 (m, γ and δ =CH), and 7.03 ppm (m, β =CH).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.75; mol wt, 182.0943. Found: C, 65.47; H, 7.52; mol wt, 182.0940 (HRMS).

Ethyl 2,4-Dimethyl-(*E*)- and -(*Z*)-2-pentenoates (47 and 48). Triethyl α-phosphonopropionate (83.3 g, 350 mmol) was added dropwise to a slurry of 8.37 g (350 mmol) of sodium hydride in 400 mL of anhydrous ether. The slurry was kept at 25 °C for 4 h, then freshly distilled isobutyraldehyde (21.7 g, 300 mmol) was added dropwise and the mixture was heated at reflux for 2 h. Water (200 mL) was added and the organic phase was separated and worked up to give, after distillation (24 in., Nester and Faust, annular Teflon spinning band column), two isomeric fractions of better than 98% isomeric purity. The lower boiling fraction [17.0 g (37%), 72.5–73.5 °C (11 Torr)] was established to be the *Z* isomer (**48**): IR (film) 1735, 1245, 1195, 1172, 1104, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) 0.96 (d, 6 H, isopropyl CH_3), 1.26 (t, 3 H, CH_3CH_2O), 1.83 (d, 3 H, CH_3C=), 3.22 (m, 1 H, CH–), 4.16 (q, 2 H, OCH_2), and 5.68 ppm (dq, 1 H, CH=).

Anal. Calcd for $C_9H_{15}O_2$: C, 69.19; H, 10.32. Found: C, 69.25; H, 10.30.

The higher boiling fraction [11.5 g (25%), 82.5–83 °C (11 Torr)] was the *E* isomer (**47**): IR (film) 1715, 1305, 1267, 1253, 1156, 1095, and 750 cm^{-1}; ^1H NMR ($CDCl_3$) 1.03 [d, 6 H, $(CH_3)_2CH$], 1.27 (t, 3 H, CH_3CH_2O), 1.86 (d, 3 H, CH_3C=), 2.60 (m, 1 H, CH), 4.22 (q, 2 H, OCH_2), and 6.64 (dq, 1 H, CH=).

Anal. Calcd for $C_9H_{15}O_2$: C, 69.19; H= []/32/ Found: C, 69.05; H, 10.15.

2,4-Dimethyl-(*E*)-2-pentenol (49). Ethyl 2,4-dimethyl-(*E*)-2-pentenoate (11.8 g, 78 mmol) (**47**) was added dropwise to a slurry of 3.0 g of lithium aluminum hydride in 200 mL of anhydrous ether. The mixture was stirred overnight, then decomposed with saturated potassium sodium tartrate. The white precipitate was filtered and the filtrate was worked up to give, after distillation, 7.0 g (82%) of the desired alcohol **49**: bp 70–71 °C (15 Torr); IR ($CHCl_3$) 3265 cm^{-1}; ^1H NMR ($CDCl_3$) 0.94 [d, 6 H, $(CH_3)_2CH$], 1.67 (d, 3 H, CH_3), 2.52 (m, 1 H, CH), 2.14 (s, 1 H, OH), 3.92 (m, 2 H, CH_2OH), and 5.23 ppm (dq, 1 H, CH=).

Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.62; H, 12.25.

2,4-Dimethyl-(*E*)-2-pentenal (50). A mixture of 13.6 g (118 mmol) of **49**, 70.0 g of activated manganese dioxide (Beacon Chemical Co.), and 400 mL of ether was stirred at 25 °C for 24 h. The solid was filtered and washed with ether, and the filtrate was concentrated at atmospheric pressure through a Vigreux column. The residue was distilled to afford 9.1 g (69%) of colorless aldehyde: bp 75–77 °C (50–55 Torr); IR ($CHCl_3$) 1700, 1650, and 1037 cm^{-1}; ^1H NMR ($CDCl_3$) 1.08 [d, 6 H, $(CH_3)_2CH$], 1.74 (d, 3 H, CH_3C=), 2.76 (m, 1 H, CH–), 6.25 (dq, 1 H, CH=), and 9.33 ppm (s, 1 H, CHO).

Anal. Calcd for $C_7H_{12}O$: C, 75.00; H, 10.78; mol wt, 112. Found: C, 74.87; H, 10.88; mol wt, 112 (mass spectrum).

Ethyl 4,6-Dimethyl-(*E,E*)-2,4-heptadienoate (51). A solution of 9.0 g (82 mmol) of **50** in 25 mL of anhydrous ether was added to 100 mmol of freshly prepared triethyl α-phosphonoacetate sodium salt in ether and the mixture was heated at reflux for 4 h. Water (200 mL) was added, the layers were separated, and the organic phase was worked up to give, after distillation, 9.0 g (61%) of dienoate **51**: bp 66–68 °C (0.5 Torr); IR ($CHCl_3$) 1722, 1636, and 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) 1.01 [d, 6 H, $(CH_3)_2CH$], 1.26 (t, 3 H, CH_3CH_2O), 1.77 (d, 3 H, CH_3), 2.70 (m, 1 H, CH), 4.14 (q, 2 H, OCH_2), 5.8 (bd, 1 H, δ =CH), 5.72 (d, 1 H, α =CH), and 7.28 ppm (d, 1 H, β =CH).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.76; H, 10.10.

4,6-Dimethyl-(*E,E*)-2,4-heptadienoic Acid (46). A mixture of 9.1 g (50 mmol) of **51**, 2.40 g (60 mmol) of sodium hydroxide, 2 mL of ethanol, and 100 mL of water was heated at reflux for 3 h, cooled, and extracted with ether. The aqueous phase was acidified and extracted with ether and the crude acid was worked up to afford 7.4 g (96%) of product (**46**). An analytical sample was prepared by chromatography (silica gel, acetone) to give a crystalline solid: mp 51 °C; IR ($CHCl_3$) 3400, 1710, 1618, and 1376 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) 1.03 [d, 6 H, $(CH_3)CH$], 1.78 (d, 3 H, CH_3), 2.70 (m, 1 H, CH), 5.79 (d, 1 H, α =CH), 5.77 (bd, 1 H, δ =CH), and 7.41 ppm (d, 1 H, β =CH).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.17; H, 9.26.

4,6-Dimethyl-(*E,E*)-2,4-heptadienoyl Chloride (18). A solution of 6.1 g (40 mmol) of **46**, 8 mL of thionyl chloride, and 100 mL of benzene was kept at 25 °C for 6 h, then concentrated in vacuo. The residue was distilled to give 5.2 g (77%) of the pale yellow acid chloride (**18**): bp 62–64 °C (2 Torr); ^1H NMR ($CDCl_3$, 100 MHz) 1.02 [d, 6 H, $(CH_3)_2CH$], 1.82 (d, 3 H, CH_3C=), 2.72 (m, 1 H, CH), 5.92 (bd, 1 H, δ =CH), 5.95 (d, 1 H, α =CH), and 7.43 ppm (d, 1 H, β =CH).

Ethyl 6,8-Dimethyl-3-oxo-(*E,E*)-4,6-nonadienoate (45). A mixture of 1.95 g (80 mmol) of magnesium shavings, 7.4 g (160 mmol) of anhydrous ethanol, and 0.5 mL of carbon tetrachloride was heated at reflux for 1 h. A solution of 5.28 g (40 mmol) of monoethyl malonate in 60 mL of dry tetrahydrofuran was added dropwise to the magnesium ethoxide paste and the mixture was heated at reflux for 4 h, then cooled. A solution of 5.18 g (30 mmol) of the dienoyl chloride **18** in 20 mL of dry tetrahydrofuran was added and the yellow solution was kept at 70 °C for 6 h. Hydrochloric acid (2 N) was added dropwise until gas evolution ceased and the product was extracted into ether. The organic extracts were washed with 5% sodium bicarbonate and worked up. The residue was distilled to give 4.4 g (66%) of light yellow ester (**45**): bp 137–142 °C (2 Torr); IR ($CHCl_3$) 1748, 1660, 1599, 1255, and 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) (keto form) 0.99

[d, $(CH_3)_2CH$], 1.23 (t, CH_3CH_2O), 1.79 (d, CH_3C=), 2.65 (m, CH), 3.55 (s, $COCH_2CO$), 4.17 (q, OCH_2), 5.78 (bd, δ =CH), 6.13 (d, α =CH), and 7.18 ppm (d, β =CH); ^{1}H NMR (enol form) 0.98 [d, $(CH_3)_2CH$], 1.26 (t, CH_3CH_2O), 1.79 (d, CH_3C=), 2.65 (m, CH-), 4.17 (q, OCH_2), 5.02 (s, *HC*=COH), 5.67 (bd, δ =CH), 6.14 (d, α =CH), and 7.03 (d, β =CH).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99; mol wt, 224.1412. Found: C, 69.24; H, 9.04; mol wt, 224.1409 (HRMS).

Ethyl Tirandamycyl-3-oxobutanoate (54). A mixture of 100 mg (0.30 mmol) of tirandamycic acid (**53**) and 7.5 mL of 0.04 N sodium hydroxide in 10 mL of *tert*-butyl alcohol was lyophilized to give the sodium salt, which was stirred at 5 °C for 10 min with a trace of dry pyridine, 0.5 mL of oxalyl chloride, and 20 mL of dry benzene. Solvent was removed in vacuo and the tirandamycyl chloride was extracted into dry benzene, filtered of sodium chloride, and concentrated to a small volume. The tirandamycyl chloride was added to a benzene slurry of ethyl sodioacetoacetate [made from 11 mg of 57% sodium hydride suspension in mineral oil and 38 mg (0.30 mmol) of ethyl acetoacetate] and the slurry was stirred at 25 °C for 2 h. Acidification (0.1 N hydrochloric acid), workup, and quick chromatography (silica gel, 2% MeOH in $CHCl_3$) gave 121 mg (92%) of product (**54**): IR ($CHCl_3$) 1728, 1704, 1620, and 1089 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) 0.74 (d, 3 H), 1.15 (d, 3 H), 1.36 (t, 3 H), 1.51 (s, 3 H), 1.61 (s, 3 H), 1.88 (s, 3 H), 2.02 (m, 1 H), 2.43 (s, 3 H), 2.86 (m, 1 H), 3.32 (s, 1 H), 3.63 (q, 1 H), 4.07 (d, 1 H), 4.38 (q, 2 H), 6.21 (d, 1 H), 6.80 (d, 1 H), and 7.57 ppm (d, 1 H).

Anal. Calcd for $C_{24}H_{32}O_8$: C, 64.28; H, 7.19; mol wt, 448.2097. Found: C, 64.47; H, 7.18; mol wt, 448.2093 (HRMS).

Ethyl Tirandamycylacetate (52). Ethyl 2-tirandamycyl-3-oxobutanoate (**54**, 90 mg, 0.2 mmol) was chromatographed four times over a column of 50 g of silica gel with 2% methanol in chloroform to afford 71.0 mg (90%) of the deacetylated product **52**: IR ($CHCl_3$) 1728, 1230, and 1150 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) (keto tautomer) 0.74 (d), 1.16 (d), 1.29 (t), 1.51 (s), 1.62 (s), 1.83 (bs), 1.99 (m), 2.84 (m), 3.32 (s), 3.62 (dd), 3.68 (s), 4.07 (d), 4.28 (q), 5.89 (bd), 6.24 (d), and 7.29 ppm (d); (enol tautomer) 0.74 (d), 1.15 (d), 1.30 (t), 1.51 (s), 1.62 (s), 1.83 (bs), 1.99 (m), 2.84 (m), 3.32 (s), 3.62 (dd), 3.68 (s), 4.07 (d), 4.28 (q), 5.16 (s), 6.16 (bd), 6.24 (d), and 7.21 ppm (d). The analytical sample was prepared by similar chromatography.

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44; mol wt, 406.1991. Found: C, 65.00; H, 7.40; mol wt, 406.1987 (HRMS).

***tert*-Butyl Sarcosinate.** A mixture of 35.6 g (400 mmol) of sarcosine and 200 mL (400 mmol) of 2 N sodium hydroxide was cooled to 0–5 °C. Benzyl chloroformate (68.5 g, 400 mmol) and 100 mL of 4 N sodium hydroxide were added simultaneously. The mixture was stirred for 2 h in the cold and at 25 °C for 2 h, then extracted with chloroform. The aqueous phase was acidified and the product was extracted into ethyl acetate and worked up to give 85.0 g (95%) of crude *N*-carbobenzoxysarcosine, which was dissolved in 300 mL of dioxane, 2 mL of concentrated sulfuric acid, and ca. 300 mL of liquefied isobutylene in a pressure bottle and sealed. The mixture was agitated for 5 days, poured into a 5% sodium bicarbonate solution, and extracted twice with chloroform. The usual workup gave the crude *tert*-butyl ester, which was shaken in a Paar hydrogenation apparatus for 1 day with 350 mL of methanol and 2 g of 5% palladium on carbon. The solution was filtered, the solvent was removed in vacuo, and the residue was distilled to afford 35.0 g (60% overall yield) of *tert*-butyl sarcosinate: bp 82–83 °C (75 Torr); IR ($CHCl_3$) 3355, 1735, 1365, 1222, and 1152 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.46 [s, 9 H, $(CH_3)_3C$], 1.53 (s, 1 H, NH), 2.40 (s, 3 H, CH_3N), and 3.22 ppm (s, 2 H, CH_2N).

Anal. Calcd for $C_7H_{15}NO_2$: C, 57.93; H, 10.34; N, 9.65. Found: C, 57.93; H, 10.43; N, 9.46.

1-Methyl-3-sorbyl-2,4-pyrrolidione (41). A mixture of 1.45 g (10 mmol) of *tert*-butyl sarcosinate, 1.83 g (10 mmol) of **44**, and 25 mL of xylene was heated at 120–125 °C for 6 h. The solvent was removed in vacuo and the residue was dissolved in methanol and treated with 10 mL of 2 N methanolic sodium methoxide. The mixture was heated at reflux for 6 h, acidified, and worked up. The residue was chromatographed (Bio-Sil A, $CHCl_3$) to give 25 mg (1%) of desired tetramate **41**, mp 85–88 °C, whose properties were identical with those of the compound prepared by acylation of **26**.

Ethyl *N*-Cyclohexylglycinate. Ethyl bromoacetate (33.4 g, 200 mmol) was added dropwise to a cooled solution of distilled cyclohexylamine (40.0 g, 410 mmol). The mixture was stirred overnight and the cyclohexylamine hydrobromide was filtered and washed with ether. The filtrate was concentrated in vacuo and the residue was distilled to afford 30.0 g (81%) of ethyl *N*-cyclohexylglycinate, bp 122–123 °C (15 Torr) [lit.[28] 111–115 °C (9 Torr)].

1-Benzyl-3-sorbyl-2,4-pyrrolidione (39). A solution of 5.46 g (30 mmol) of ethyl 3-oxo-(*E,E*)-4,6-octadienoate (**44**), 5.79 g (30 mmol) of ethyl *N*-benzylglycinate,[26] and 45 mL of xylene was heated at 120–125 °C for 16 h. The orange solution was added dropwise to an ethanolic sodium ethoxide solution (1.15 g of sodium metal in 25 mL of anhydrous ethanol), then heated at 70 °C for 8 h. The tan precipitate was collected, washed with benzene, suspended in water (75 mL), and acidified with 3 N hydrochloric acid. The suspension was extracted with chloroform and the extracts were worked up to give a dark brown oil. Chromatography (Bio-Sil A, $CHCl_3$) gave 120 mg of starting β-keto ester and 2.60 g (30%, based on unrecovered β-keto ester) of crystalline yellow product (**39**): mp 100.5–101.5 °C; IR ($CHCl_3$) 1700, 1630, 1566, 1470, 1250, and 1000 cm^{-1}; ^{1}H NMR, see Table I.

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94; mol wt, 283.1208. Found: C, 72.07; H, 6.01; N, 5.05; mol wt, 283.1201 (HRMS).

1-Cyclohexyl-3-sorbyl-2,4-pyrrolidione (56). A solution of 7.4 g (40 mmol) of ethyl *N*-cyclohexylglycinate, 7.28 g (40 mmol) of **44**, and 70 mL of toluene was heated at reflux for 4 h, then added to an ethanolic sodium ethoxide solution (1.15 g of sodium metal in 30 mL of ethanol). The reaction mixture was heated at reflux for 1.5 h and diluted with water. The layers were separated and the aqueous phase was acidified, extracted with chloroform, and worked up to give an orange solid. Recrystallization from acetone–hexane gave 5.3 g (48%) of yellow platelets (**56**): mp 184–185 °C; IR (KBr) 1710, 1665–1610, 1570, 1478, 1244, and 1005 cm^{-1}; ^{1}H NMR, see Table I.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.80; H, 7.69; N, 5.08; mol wt, 275.1522. Found: C, 69.65; H, 7.67; N, 5.20; mol wt, 275.1523 (HRMS).

1-(*p*-Methoxybenzyl)-3-sorbyl-2,4-pyrrolidione (57). A solution of 17.5 g (96 mmol) of **44**, 22.5 g (100 mmol) of ethyl *N*-(*p*-methoxybenzyl)glycinate, and 100 mL of xylene was heated at 120–125 °C for 10 h. The crude β-keto amide was added dropwise to an ethanolic sodium ethoxide solution (2.3 g of sodium metal in 100 mL of anhydrous ethanol). The reaction mixture was stirred at 25 °C for 6 h, acidified, and extracted with chloroform. The extracts were worked up to give a dark brown oil, which was chromatographed (Bio-Sil A, C_6H_6) to give the starting β-keto ester (2.5 g), followed by product (**57**). The yellow solid was recrystallized from acetone–hexane to afford 9.0 g (35%, based on unrecovered ester) of lemon-yellow crystals (**57**): mp 116–117 °C; IR ($CHCl_3$) 1700, 1625, 1570, 1470, 1246, and 1005 cm^{-1}; ^{1}H NMR, see Table I. The mother liquors were combined with the early and late chromatographic fractions and rechromatographed over Bio-Sil A to give an additional 2.0 g (8%) of product.

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47; mol wt, 313.1314. Found: C, 68.84; H, 5.82; N, 4.35; mol wt, 313.1320 (HRMS).

1-(*p*-Methoxybenzyl)-3-[4,6-dimethyl-(*E,E*)-2,4-heptadienoyl]-2,4-pyrrolidione (58). A mixture of 1.13 g (5 mmol) of **45**, 1.13 g (5 mmol) of ethyl *N*-(*p*-methoxybenzyl)glycinate, and 25 mL of xylene was heated at 125–130 °C for 8 h. The β-keto amide solution was added to 10 mL of 1 N ethanolic sodium ethoxide and heated at reflux for 1 h. Water (100 mL) was added, the layers were separated, and the aqueous phase was acidified and extracted with chloroform. The organic extracts were worked up and chromatographed (Bio-Sil A, C_6H_6) to give 480 mg (26%) of lemon-yellow, crystalline product **58**: mp 94–100 °C; IR ($CHCl_3$) 1698, 1615, 1565, 1515, 1474, and 1246 cm^{-1}; ^{1}H NMR, see Table I.

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.91; mol wt, 355.1783. Found: C, 70.87; H, 7.12; N, 3.73; mol wt, 355.1783 (HRMS).

3-Sorbyl-2,4-pyrrolidione (59). A solution of 2.03 g (6.16 mmol) of **57** and 35 mL of trifluoroacetic acid was kept at 25 °C for 96 h, then poured into ice water. The precipitate was collected, washed with water and ether, and air dried. Recrystallization from acetone–hexane gave 1.05 g (80%) of orange-yellow solid (**59**): mp 211–212 °C; IR (KBr) 3440, 1680, 1628, 1574, 1465, 1255, and 1000 cm^{-1}; ^{1}H NMR, see Table I.

Anal. Calcd for $c_{10}H_{11}NO_3$: C, 62.10; H, 5.75; N, 7.25; mol wt, 193.0739. Found: C, 61.90; H, 5.87; N, 7.03; mol wt, 193.0735 (HRMS).

3-Acetyl-1-benzyl-2,4-pyrrolidione (29) from *N*-Benzylaminoace-

tonitrile. Procedure A. A solution of 7.3 g (50 mmol) of *N*-benzylaminoacetonitrile, 60 mL of benzene, and 4.2 g (50 mmol) of distilled diketene was stirred at 25 °C for 2 h and concentrated in vacuo. The yellow, oily residue was chromatographed (silica gel, $CHCl_3$) to give 10.5 g (91%) of ***N*-acetoacetyl-*N*-benzylaminoacetonitrile (60):** ^1H NMR ($CDCl_3$) 1.98 (s, CH_3, enol), 2.30 (3 H, s, CH_3CO), 3.67 (2 H, s, $C_6H_5CH_2$), 4.20 (2 H, s, CH_2CN), 4.65 (2 H, s, $COCH_2CO$), 5.23 (bs, =CH, enol), 7.3 (5 H, bs, C_6H_5).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.16; mol wt, 230. Found: C, 67.72; H, 6.12; N, 12.06, mol wt, 230 (mass spectrum).

A solution of 1.15 g (5 mmol) of **60**, 1.00 g (5.5 mmol) of *p*-toluenesulfonic acid monohydrate, and 25 mL of ethanol was heated at reflux for 4 h and concentrated in vacuo. The residue was worked up and chromatographed (silica gel, $CHCl_3$) to give 1.15 g (80%) of acetoacetyl ester, which was treated with 6 mL of 1 N ethanolic sodium ethoxide in 25 mL of benzene. The reaction mixture was heated at reflux for 2 h, cooled, diluted with water, and worked up to give, after recrystallization from benzene–cyclohexane, 810 mg (70% yield, based on starting nitrile) of **29**, whose properties were identical with those of the product obtained above from ethyl *N*-benzylglycinate.

Procedure B. A solution of 3.65 g (25 mmol) of *N*-benzylaminoacetonitrile, 2.1 g (25 mmol) of distilled diketene, and 70 mL of anhydrous ether was kept at 25 °C for 3 h and concentrated in vacuo. The residue (**60**) was dissolved in 60 mL of dry 1,2-dimethoxyethane under nitrogen, cooled to −78 °C, treated with 13 mL of 2.04 N *n*-butyllithium in hexane, and heated at reflux for 24 h. The yellow mixture was diluted with water, washed with chloroform, acidified, and extracted with ether. The ethereal extracts were worked up and chromatographed (silica gel, C_6H_6) to give 2.34 g (40%) of the acetyl tetramate **29**, mp 68–69 °C, whose physical and spectroscopic properties were identical with those of the product obtained in A via cyclization of the acetoacetyl ester above.

3-Acetyl-1-methyl-2,4-pyrrolidione (30) from *N*-Methylaminoacetonitrile. Procedure B of the previous section was followed, employing 3.5 g (50 mmol) of *N*-methylaminoacetonitrile,[29] 4.2 g (50 mmol) of distilled diketene, and 26 mL of 2.04 M *n*-butyllithium in hexane to give 3.00 g (38%) of **30**, whose properties were identical with those of the product obtained starting from ethyl sarcosinate (cf. above).

1-Methyl-3-sorbyl-2,4-pyrrolidione (41) from *N*-Methylaminoacetonitrile. A SOLUTION OF [/4] G (20 mmol) of *N*-methylaminoacetonitrile,[29] 1.82 g (10 mmol) of **44**, and 30 mL of xylene was heated at 125 °C for 6 h and concentrated in vacuo. The residue was dissolved in 25 mL of ethanol containing 2.00 g (11 mmol) of *p*-toluenesulfonic acid monohydrate, heated at reflux for 4 h, and concentrated in vacuo. The esterified residue was taken up in chloroform, washed free of acid, dried, and concentrated. The residue was dissolved in 25 mL of benzene, treated with 12 mL of 1 N ethanolic sodium ethoxide, and heated at reflux for 2 h. After workup, chromatography (Bio-Sil A, $CHCl_3$) gave 100 mg (5%) of the desired tetramate **41**, mp 85–89 °C, with spectroscopic properties identical with those of the same product obtained by other routes (cf. above).

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