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Synthetic Applications of *N*-Acylamino-1,3-dienes. An Efficient Stereospecific Total Synthesis of *dl*-Pumiliotoxin C, and a General Entry to *cis*-Decahydroquinoline Alkaloids[1]

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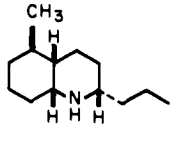
Abstract: Two efficient total syntheses of *dl*-pumiliotoxin C (**1**) are reported. A Diels–Alder strategy is employed which features the use of *trans*-1-*N*-acylamino-1,3-butadienes as synthetic equivalents for *trans*-1-amino-1,3-butadiene. In the best approach (Scheme II), **1** was prepared in a stereospecific fashion in three steps, and greater than 50% overall yield, from benzyl *trans*-1,3-butadiene-1-carbamate (**19**). The efficient preparation of other dialkyl *cis*-decahydroquinolines by this general synthetic strategy (Scheme III) is also reported.

Extensive investigations[3] of the toxic skin secretions of neotropical "poison-dart" frogs of *Dendrobates pumilio*,[4,5] *Dendrobates auratus*,[6] and *Dendrobates histrionicus*[7] have resulted in the isolation of more than 60[8] pumiliotoxins. The first member of this alkaloid group to be characterized was pumiliotoxin C, which was shown by x-ray analysis of the hydrobromide[4,7] to have the unusual *cis*-decahydroquinoline structure **1**.[9] Subsequently, a number of dendrobatid alkaloids (the pumiliotoxin C and hydroxypumiliotoxin C classes) have been tentatively assigned similar decahydroquinoline structures,[7,8] for example, alkaloids I (**2**), II (**3**), and III (**4**).[7,8]



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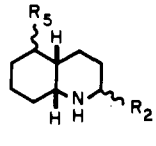
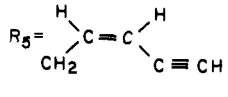


2, R_2 = n-C_4H_9, R_5 = H

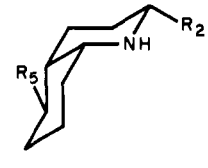
3, $R_2 = R_5$ = n-C_3H_7

4, $R_2 = (CH_2)_3CH{=}C{=}CH_2$



Alkaloids of the pumiliotoxin C class having a variety of saturated and unsaturated side chains, with lengths up to nine carbons, have been recognized.[8] The *cis*-decahydroquinoline ring is also a structural feature of the tricyclic dendrobatid alkaloids of the gephyrotoxin family.[7,8] The impossibility of isolation of more than milligram quantities of these toxins from natural sources, together with their significant neurological activities,[4,5,7,8,10] makes these alkaloids attractive targets for total synthesis.

A successful synthesis of alkaloids of the pumiliotoxin C class must deal with construction of the *cis*-decahydroquinoline ring,[11] and elaboration of the correctly oriented side chains at carbons 2 and 5. For alkaloids with the pumiliotoxin C stereochemistry, the two side chains are equatorially oriented in the most stable *cis*-decahydroquinoline conformation **5**.



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Synthetic efforts to date have focused on pumiliotoxin C, culminating in a number of successful total syntheses.[11b,12,13] In this paper we present details of our total synthesis of racemic pumiliotoxin C,[14] which provides an excellent illustration of the application of *N*-acylamino-1,3-dienes[15,16] for solving formidable stereochemical problems in the alkaloid area. The generalization of this route to the synthesis of other pumiliotoxins and pumiliotoxin analogues is also detailed.

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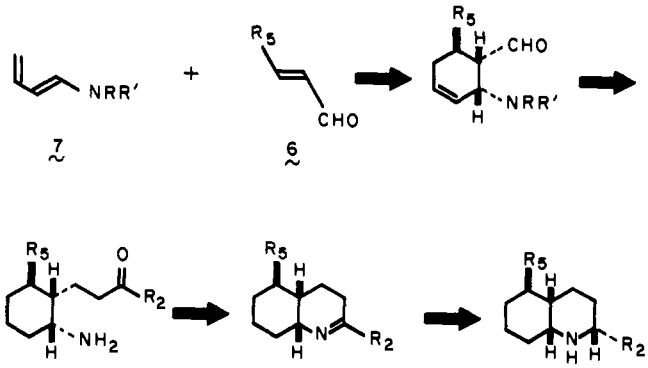
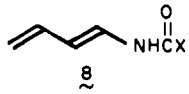
Scheme I



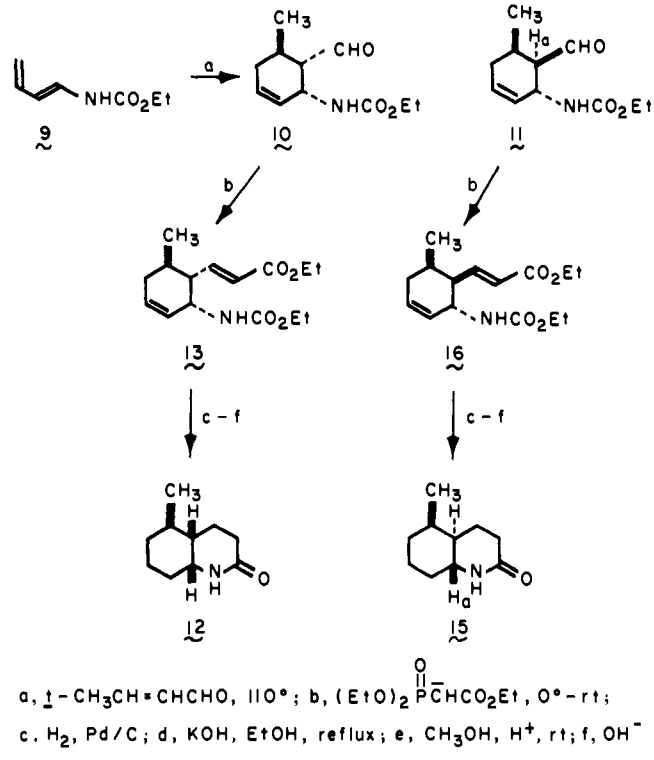
Results and Discussion

Synthetic Strategy. Our synthetic plan called for cycloaddition of a trans enal (**6**) with a suitably masked *trans*-1-amino-1,3-butadiene (**7**), followed by elaboration of the heterocyclic ring as outlined in Scheme I.[17] The stereochemical strategy was to take advantage of the stereoselectivity of the Diels–Alder reaction to establish the three chiral centers of the carbocyclic ring, and to utilize these centers to control the introduction of the chiral center at carbon 2. The central issue of this projected synthesis was whether or not a highly endo-stereoselective cycloaddition could be accomplished. It is well known that the introduction of a trans methyl at carbon 3 of an acrylate dienophile reduces endo stereoselectivity in cycloadditions with cyclopentadiene.[18] Thus, we assumed at the outset that a reactive diene would be required.[19]

Diels–Alder Reaction of *trans*-1-*N*-Acylamino-1,3-butadienes with *trans*-Crotonaldehyde. Preparation of Endo Adduct 10. A suitably reactive *trans*-1-amino-1,3-butadiene synthetic equivalent (**7**) was required.[16] Although 1-phthalimido-1,3-butadiene is known, its preparation is multistep and inefficient.[20] Faced with the availability of no satisfactory synthetic equivalents of this type,[21] we examined the possibility of employing *trans*-1-*N*-acylamino-1,3-butadienes **8**. These

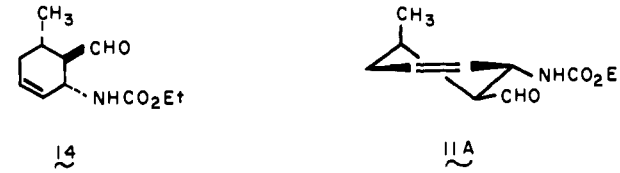


dienes embody the attractive feature that their reactivity can potentially be manipulated by variations in the acyl substituent X. Recent reports from our laboratory have described the preparation[15] and cycloaddition reactivity[19] of a variety of acylaminobutadienes. Our initial attention, therefore, focused on reactions of **8** with dienophiles of the *trans*-crotonate family. Although *trans*-1-trichloroacetamido-1-3-butadiene (**8**, X = CCl_3) readily undergoes Diels-Alder reaction with acrolein[15a] or methyl acrylate[19] at 110 °C, we were unsuccessful in obtaining significant amounts of cycloadducts with less reactive crotonate dienophiles, including *trans*-crotonaldehyde, methyl *trans*-crotonate, and crotonyl chloride. However, to our delight, the slightly more reactive diene carbamate **9**[15b,c] reacted satisfactorily. Thus when **9** was heated at 110 °C with neat *trans*-crotonaldehyde for 2.5 h, a single crystalline cycloadduct **10**, mp 59–60 °C (^{1}H NMR δ 9.69), was isolated in 61% yield, together with 10–15% of unreacted diene **9**. HPLC analysis of the crude cycloaddition product indicated that less than 10% of isomeric Diels-Alder adducts was present after 2.5 h. However, when this cycloaddition was carried out for a longer time, or at a higher temperature, a second cycloadduct **11** (^{1}H NMR δ 9.79) was formed in significant amounts. The supposition that the initially formed adduct **10** was the desired product resulting from endo cycloaddition was unambiguously established by its transformation to the known[12b,c] cis-fused



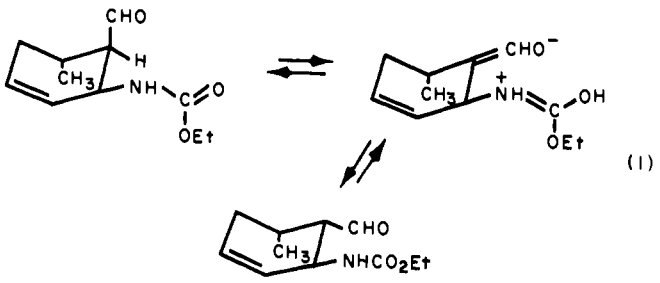
a, *t*-$CH_3CH{=}CHCHO$, 110°; b, $(EtO)_2\overset{O}{\overset{\|}{P}}\bar{C}HCO_2Et$, 0°–rt; c, H_2, Pd/C; d, KOH, EtOH, reflux; e, CH_3OH, H^+, rt; f, OH^-

lactam **12**, mp 151–152 °C, which was identical with a sample provided by Professors Ibuka and Inubushi. This conversion was accomplished by treatment of **10** in tetrahydrofuran (THF) with the sodium salt of triethyl phosphonoacetate, initially at 0 °C and subsequently at room temperature, to afford the crystalline ester **13**. Catalytic hydrogenation of **13**, followed by alkaline hydrolysis, and cyclization yielded **12**. Conducting the phosphonate anion olefination at reflux in benzene[22] resulted in partial epimerization of **10**, with the subsequent formation of a mixture of unsaturated esters. The NMR spectra of the adduct formed at long reaction times indicated that it was not the stereoisomer resulting from exo cycloaddition. In particular the absorption for the ring methyl at 16.6 ppm in the carbon spectrum, which is in the range of an axial CH_3,[23] and the absorption for H_a in the 220-MHz proton spectrum, an unresolved multiplet at δ 2.5 with a half-height width of 15 Hz, were inconsistent with structure **14**, which would have all three ring substituents equatorial. These data were more consistent with structure **11**, which, in its most stable conformation **11A**, would have an axial methyl and only



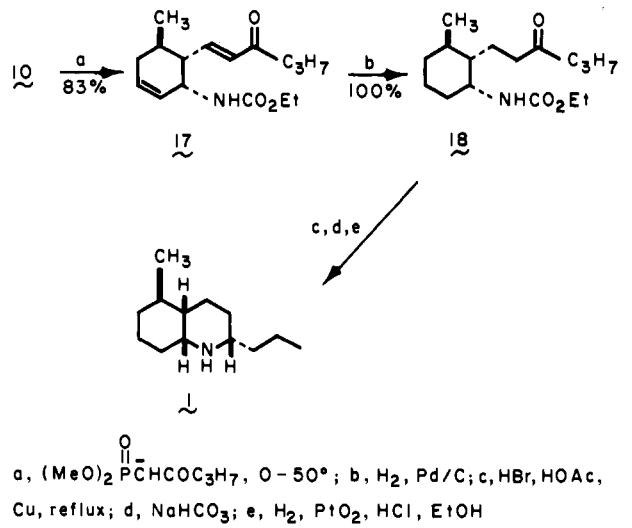
one axial–axial coupling for proton H_a.[24] This tentative assignment was confirmed by converting **11** to the trans-fused lactam **15**, mp 141.5–142 °C. The structure of **15** followed unambiguously[23,24] from its NMR spectra: the axial proton H_a was observed as a broad multiplet (half-height width = 22 Hz) in the proton spectrum, and the axial methyl at 12.9 ppm in the carbon spectrum.

The unexpectedly facile conversion of the endo adduct **10** to **11** likely involves the neighboring acylamino function. We believe that this epimerization may result from participation of the acylamino group as an intramolecular general base, eq 1.[25] The related epimerization of the cis adducts resulting from the Diels–Alder reaction of dienamides **8** and acrylate dienophiles has also been observed.[19,26]



(1)

Conversion of Diels–Alder Adduct 10 to *dl*-Pumiliotoxin C. Addition of the required five carbon atoms to the endo adduct **10** was accomplished by the Horner–Wadsworth–Emmons procedure.[22] Reaction of **10** with 1–2 equiv of the sodium salt of dimethyl 2-oxopentylphosphonate[27] proceeded smoothly to afford the crystalline enone **17**, mp 102.5–104 °C, in 83% yield. To avoid epimerization, it was again essential to add the phosphonate carbanion to the aldehyde at low temperature, and subsequently raise the temperature to promote fragmentation of the resulting adduct. Hydrogenation of **17** at atmo-



a, $(MeO)_2\overset{O}{\overset{\|}{P}}\bar{C}HCOC_3H_7$, 0–50°; b, H_2, Pd/C; c, HBr, HOAc, Cu, reflux; d, $NaHCO_3$; e, H_2, PtO_2, HCl, EtOH

spheric pressure over Pd/C suffered no complication from competing hydrogenolysis of the allylic amide,[28] and yielded **18** quantitatively. Our initial attempts to deprotect the amino group of **18** by treatment with either ethanolic KOH or commercially available 30% HBr in acetic acid were not successful. We speculated that the problem with the HBr cleavage was competing α-bromination of the ketone, and therefore chose to carry out this reaction in the presence of copper powder, which should rapidly reduce any bromine present. With this modification the HBr and acetic acid cleavage worked well, and after concentration and partitioning of the resulting residue between ether and saturated aqueous bicarbonate the sensitive $\Delta^{1,2}$ imine was produced. The crude imine was immediately hydrogenated in acidic ethanol[12f] to afford, after trituration with hexane, pure *dl*-pumiliotoxin C hydrochloride, mp 232–234 °C (mp 243–244 °C after one recrystallization from 2-propanol) in 83% yield from **18**. Synthetic pumiliotoxin C hydrochloride was identical by mixture melting point, IR, ^1H and ^{13}C NMR, and GC with authentic samples of racemic pumiliotoxin C hydrochloride kindly provided by Professors Ibuka, Inubushi, and Habermehl.

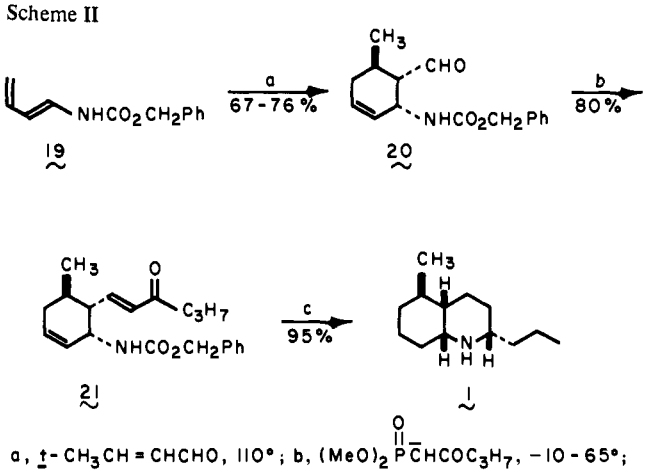
A Three-Step Stereospecific Total Synthesis of *dl*-Pumiliotoxin C from Diene 19. Our approach for the synthesis of alkaloids of the pumiliotoxin C family would be significantly simplified if amine unmasking were accomplished under hydrogenation conditions (Scheme II). To this end the reaction of benzyl *trans*-1,3-butadiene-1-carbamate (**19**)[15c] and *trans*-crotonaldehyde was investigated. Diene **19** cleanly

Table I. ^1H NMR Analysis of the Reaction of Diene **19** and *trans*-Crotonaldehyde

		product composition[a]		
temp, °C	time, h	endo adduct **20** (δ 9.68)	"low field" adducts (δ 9.78 and 9.83)	"low field" adduct ratio unknown (δ 9.83): endo epimer (δ 9.78)
110	0.67	97	<3	>4:1
110	1.0	96	4	3:1
110	1.3	95	5	3:2
110	2.7	90	10	1:1
110	12.	45	55	1:9
140	0.3	85	15	2:1
140	0.5	70	30	1:2
140	0.7	60	40	1:4
25	30	80[b]	20[b]	>5:1[c]
25	96	80[b]	20[b]	>5:1[c]
25	144	80[b]	20[b]	>5:1[c]

[a] By FT ^1H NMR analysis at 90 MHz. Estimated error ±5–10%. [b] These values are less reliable since they correspond to very low conversion to the cycloadduct. No more than 20% of cycloadduct was formed at 144 h. [c] δ 9.78 absorption was not detected.

Scheme II

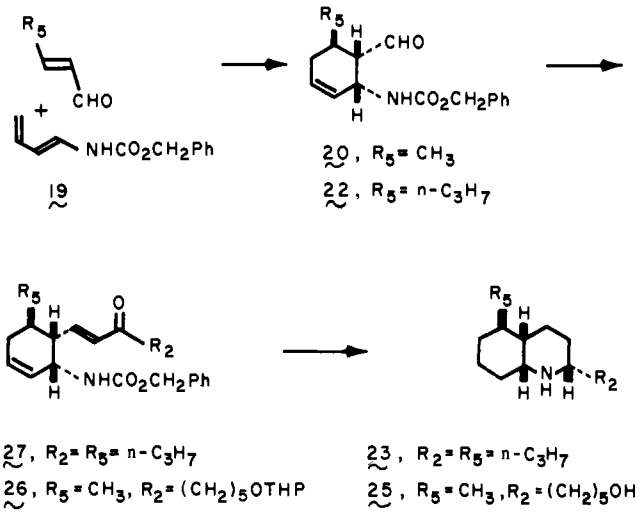


a, *t*-CH_3CH=CHCHO, 110°; b, $(MeO)_2\overset{O}{\overset{\|}{P}}\bar{C}HCOC_3H_7$, −10–65°; c, H_2, Pd/C, HCl, EtOH

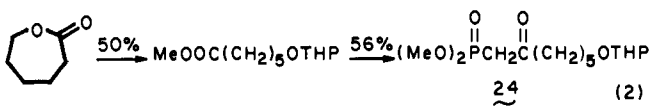
undergoes cycloaddition with *trans*-crotonaldehyde at 110 °C to afford the crystalline adduct **20**, mp 74–75 °C (^1H NMR δ 9.68), in 67% yield (76% based on recovered and reused diene). As was observed in the cycloaddition of diene **9**, at long reaction times an additional adduct (^1H NMR δ 9.78), presumed to be the epimer at the formyl-bearing carbon, was also formed. Careful ^1H NMR analysis (90 MHz) of the crude Diels–Alder reaction mixture indicated that after 160 min at 110 °C the cycloaddition was *remarkably stereoselective*[29] as no more than 10% of other isomers was present. These results, together with the results of similar investigations of the cycloaddition stereoselectivity at other temperatures, are summarized in Table I (Experimental Section). Phosphonate anion olefination of **20** afforded the crystalline enone **21**, mp 75–76 °C, in 80% yield. When **21** was hydrogenated at atmospheric pressure in the presence of just less than 1 equiv of HCl, racemic pumiliotoxin C hydrochloride, mp 241–242 °C, was isolated in 95% yield after one recrystallization from 2-propanol. This procedure thus achieves the stereospecific total synthesis of racemic **1** in three steps and 51% overall yield (58% based on consumed diene) from the benzyloxycarbonyl-protected aminobutadiene **19**.

A General Route for the Synthesis of *cis*-Decahydroquinolines of the Pumiliotoxin C Type. *cis*-Decahydroquinolines, with a variety of side chains at carbons 2 and 5, are easily

Scheme III



prepared from diene **19**. Two examples are summarized in Scheme III. Diels–Alder reaction of **19** with commercially available *trans*-2-hexen-1-al proceeded satisfactorily at 110 °C to give, as the major product, the endo adduct **22**. Olefination and hydrogenation afforded the dipropyl *cis*-decahydroquinoline **23**, mp 198–199 °C (hydrochloride salt), in 56% overall yield from diene **19**. The mass spectrum of **23** was similar to that reported[7] for alkaloid II (**3**), and a direct comparison awaits the isolation of additional amounts of the natural alkaloid.[10] Ketophosphonate **24**, which was required for the synthesis of the hydroxylated *cis*-decahydroquinoline **25**, was prepared in moderate yield from 6-hexanolactone as outlined in eq 2.[39] Olefination of **20** with the sodium salt of **24**



(2)

afforded the dienone carbamate **26**, which was converted to **25**, mp 69–70 °C (free base), in 43% overall yield from **19** by catalytic hydrogenation and alcohol deprotection. The structures assigned to *cis*-decahydroquinolines **23** and **25** follow from their mode of synthesis and their NMR spectra, which are very similar to those of pumiliotoxin C: the angular C_{8a} hydrogen was observed as a narrow multiplet (half-height width = 7–10 Hz) in the proton spectrum, and the carbon spectrum showed characteristic[30,31] peaks at 56–60 ppm for carbons 2 and 8a.

The synthesis of other pumiliotoxin C analogues and the results of their neuropharmacological evaluation will be reported elsewhere.

Conclusion

Racemic pumiliotoxin C was synthesized in a stereospecific fashion, in three steps and greater than 50% overall yield, from acylaminobutadiene **19**. *N*-Acylamino-1,3-diene synthetic methodology significantly simplifies the construction of *cis*-decahydroquinolines of the pumiliotoxin C type, and should be useful for the synthesis of other *cis*-decahydroquinoline alkaloids.

Experimental Section[32]

Cycloaddition of Ethyl *trans*-1,3-Butadiene-1-carbamate (9) and *trans*-Crotonaldehyde. A. Preparation of Endo Adduct 10. A solution of **9**[15b,c] (2.82 g, 20 mmol), 4-*tert*-butylcatechol (50 mg), and 20 mL of freshly distilled *trans*-crotonaldehyde was heated at 110 °C in a sealed glass ampule for 2.5 h. Concentration and filtration of the residue through a short plug of silica gel (4:1 hexane–ethyl acetate) afforded 4 g of a colorless oil. HPLC[34] and ^{1}H NMR analysis of this material showed that one cycloadduct (**10**, CHO δ 9.69) predominated to the extent of greater than 90%, and that ca. 15% of **9** was unreacted. Purification of this oil by chromatography on silica gel (100 g, 4:1 ethyl acetate–hexane) and crystallization from hexane–ether afforded 2.56 g (61%) of the endo adduct **10**, mp 57–59 °C. Two recrystallizations from hexane–ether yielded an analytical specimen: mp 59–60 °C; ν_{max} (Nujol) 3280, 1710, 1670, and 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ) 9.69 (d, J = 1.9 Hz, CHO), 5.4–5.9 (m, C*H*=C*H*), 4.8–5.2 (m, NH), 4.3–4.7 (m, half-height width = 14 Hz, C*H*NH), 4.10 (q, J = 7.1 Hz, OCH_2), 2.2–2.6 (m, C*H*CHO), 1.23 (t, J = 7.1 Hz, CH_2CH_3), 1.09 (d, J = 6.3 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$, δ) 203.0, 156.0, 129.2, 126.2, 61.2, 56.4, 45.1, 31.4, 25.3, 19.3, 14.6; mass spectrum 211.120 (10%, $C_{11}H_{17}NO_3$ requires 211.121), 141 (100%), 95 (69%), 90 (41%). Similar cycloadditions carried out at 110 °C for 12 and 72 h resulted in the formation of adducts **10** and **11** in the ratios (HPLC analysis)[34] of 3:2 and 1:1, respectively.

B. Isolation of Epimerized Adduct 11. A solution of **9** (141 mg, 1 mmol), *trans*-crotonaldehyde (210 mg, 3 mmol), 4-*tert*-butylcatechol (10 mg), and 1 mL of dry dioxane was heated at 140 °C in a sealed ampule for 6 h. Concentration and filtration of the residue through a short plug of silica gel (4:1 hexane–ethyl acetate) yielded a colorless liquid. HPLC analysis[34] indicated that this sample was a 1:1:2 mixture (increasing k') of **10**, an unknown component, and **11**, respectively. Preparative HPLC[35] using two solvent systems (9:1 hexane–ether and 9:1 hexane–ethyl acetate) resulted in the isolation of 39 mg (18%) of **10** and 59 mg (28%) of **11**. Chromatographically homogeneous **11** was obtained as a colorless oil: ν_{max} (film) 3320, 1710, 1690, and 1530 cm^{-1}; ^{1}H NMR (220 MHz, $CDCl_3$, δ) 9.79 (d, J = 1.6 Hz, CHO), 5.3–5.9 (m, C*H*=C*H*), 4.6–4.9 (broadened d, NH), 4.2–4.5 (m, half-height width = 16 Hz, C*H*NH), 4.12 (q, J = 7.0 Hz, OCH_2), 2.3–2.6 (m, half-height width = 15 Hz, C*H*CHO, confirmed by decoupling), 1.24 (t, J = 7.0 Hz, CH_2CH_3), 1.13 (d, J = 6.5 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$, δ) 203.1 (d), 155.9 (s), 129.6 (d), 125.6 (d), 60.9 (t), 55.8 (d), 45.2 (d), 31.4 (t), 26.9 (d), 16.6 (q), 14.4 (q); mass spectrum 211.119 (9%, $C_{11}H_{17}NO_3$ requires 211.121), 141 (100%), 95 (61%), 90 (50%).

Conversion of Endo Adduct 10 to (4aα,5α,8aα)-5-Methyloctahydro-2(1*H*)-quinolone (Lactam 12). A rapidly stirred suspension of sodium hydride (340 mg, 14.2 mmol) and 50 mL of THF was treated dropwise with triethyl phosphonoacetate (3.35 g, 14.9 mmol) at 0 °C. The resulting thick paste was stirred for an additional 15 min, and then treated dropwise at 0 °C, over 5 min, with a solution of **10** (1.00 g, 4.74 mmol) and 10 mL of THF. The cooling bath was removed and the solution was stirred at room temperature for 24 h. Concentration afforded a thick paste which was filtered through a short plug of silica gel (4:1 hexane–ethyl acetate) to yield 2.45 g of a yellow oil. Purification by chromatography on silica gel (100 g, 4:1 hexane–ethyl acetate) afforded 1.01 g (76%) of chromatographically homogeneous **13**, which crystallized upon standing. Recrystallization from ether–hexane yielded an analytical specimen, mp 90–91 °C, mass spectrum 281.163 ($C_{15}H_{23}NO_4$ requies 281.163).[38]

A solution of diene ester **13** (900 mg, 3.20 mmol) and 50 mL of ethanol was hydrogenated (1 atm, 25 °C, 50 mg of 10% palladium on carbon) and filtered through a short plug of silica gel (4:1 hexane–ethyl acetate) to afford 830 mg (91%) of the corresponding saturated carbamate ester, a colorless liquid, mass spectrum 285.197 ($C_{15}H_{27}NO_4$ requires 285.194). A portion of this sample (340 mg, 1.19 mmol) was dissolved in 15 mL of 4 M ethanolic KOH, and the solution was degassed[33] and heated at reflux under a nitrogen atmosphere for 2 h. The reaction mixture was cooled to ca. 0 °C, acidified with concentrated HCl, and concentrated (bath temperature <40 °C). The residue was then refluxed overnight with 50 mL of dry methanol which contained 0.5 mL of concentrated H_2SO_4. After concentration the residue was dissolved in 15 mL of water and extracted with three 20-mL portions of ether. The aqueous layer was then carefully basified, saturated with NaCl, and extracted with three 50-mL portions of ether, and the ether extracts were dried (K_2CO_3). Concentration afforded 160 mg (80%) of **12** (ca. 90% pure by ^{13}C NMR) as a crystalline, white solid. Recrystallization from hexane–ether afforded an analytical specimen of lactam **12**: mp 151–152 °C; ^{1}H NMR ($CDCl_3$, δ) 6.0 (broad s, NH), 3.63 (m, half-height width = 7 Hz, C*H*NH), 0.93 (d, J = 5.9 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$, δ) 173.5, 52.4, 39.8, 33.7, 31.7, 27.9, 27.2, 23.1, 20.1, 19.4; mass spectrum 167.130 (24%, $C_{10}H_{17}NO$ requires 167.131), 124 (100%). This sample was identical with a sample provided by Inubushi and Ibuka on the basis

of mixture melting point and by comparison of IR and ^1H and ^{13}C NMR spectra.

Conversion of Adduct 11 to (4aα,5β,8aβ)-5-Methyloctahydro-2(1*H*)-quinolone (Lactam 15). Following a procedure similar to that described for the preparation of **13,** 480 mg (2.3 mmol) of **11** was converted to 360 mg (56%) of chromatographically homogeneous enone **16,** a colorless oil.[38] A portion of this sample of **16** (270 mg, 0.96 mmol) was hydrogenated and lactamized (as described for the preparation of **12**) to afford, after recrystallization from hexane–ethyl acetate, 70 mg (44%) of lactam **15**: mp 141.5–142 °C; ν_{max}(Nujol) 3300, 3190, 3070, 1685, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 5.6 (broad s, NH), 3.1 (m, half-height width = 22 Hz, C*H*NH), 0.90 (d, J = 7.3 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, δ) 172.1, 51.7, 42.8, 34.4, 32.8, 32.0, 31.8, 25.6, 18.9, 12.9; mass spectrum 167.130 (22%, $C_{10}H_{17}NO$ requires 167.131), 141 (50%), 124 (100%).

Conversion of Endo Adduct 10 to *dl*-Pumiliotoxin C. A. Preparation of Dienone Carbamate 17. A rapidly stirred suspension of sodium hydride (370 mg, 15.4 mmol) and 50 mL of THF was treated dropwise at −10 °C over 5 min with dimethyl 2-oxopentylphosphonate[27] (3.20 g, 16.5 mmol). The resulting suspension was stirred for an additional 20 min at −10 °C, and then treated dropwise over 5 min with a solution of **10** (1.40 g, 6.63 mmol) and 50 mL of THF. After maintaining the rapidly stirred reaction mixture for an additional 20 min at −10 °C, the cooling bath was removed and the mixture was allowed to warm to room temperature and then heated at reflux for 1 h. The reaction mixture was partitioned between ether (100 mL) and 1 M NaOH (100 mL), and the aqueous layer was extracted two additional times with ether. The ether extracts were washed with brine, dried (K_2CO_3), and concentrated to give 1.86 g of a pale yellow, crystalline solid. Recrystallization from ether–hexane (ca. 1:5) afforded 1.55 g (83%) of pure **17**: mp 102.5–104 °C; ν_{max} (Nujol) 3320, 1710, 1660, and 1530 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 6.70 (dd, J = 16.1 and 9.5 Hz, C*H*=CHCO), 6.15 (d, J = 16.1 Hz, = CHCO), 5.6–6.0 (m, C*H*=CH), 4.0–4.9 (m, NH and C*H*NH), 4.09 (q, J = 7.1 Hz, OCH_2), 2.52 (t, J = 7.1 Hz, CH_2CO), 1.22 (t, J = 7.1 Hz, OCH_2CH_3), 0.94 (d, J = 6.2 Hz, CHCH_3), 0.93 (t, J = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, δ) 200.4, 156.0, 146.2, 132.4, 129.6, 126.4, 61.0, 48.3 (2 C), 42.0, 32.4, 28.5, 19.9, 17.7, 14.6, 13.8; mass spectrum 279.181 (4%, $C_{16}H_{25}NO_3$ requires 279.183), 142 (10%), 141 (100%).

B. Preparation of *dl*-Pumiliotoxin C(1). A solution of dienone **17** (1.00 g, 3.58 mmol) and 200 mL of ethanol was treated with hydrogen (1 atm) at room temperature in the presence of 100 mg of 10% palladium on carbon. The theoretical amount of hydrogen was adsorbed in 30 min, and the mixture was filtered through Celite and concentrated to give 1.0 g (100%) of **18,** a colorless liquid, mass spectrum 283.212 ($C_{16}H_{29}NO_3$ requires 283.215). A portion of this sample (250 mg, 0.88 mmol) and 1.0 g of copper powder (freshly washed with acetic acid) was refluxed with 10 mL of freshly prepared saturated HBr in acetic acid. After 3 h the reaction mixture was concentrated, and the residue stirred for 15 min with 100 mL of saturated $NaHCO_3$ and 100 mL of ether. The ether layer was dried (K_2CO_3) for 15 min and concentrated to afford the labile $\Delta^{1,2}$ imine, which was immediately dissolved in 100 mL of a 1:1 mixture of ethanol and 2 M HCl and treated with hydrogen (1 atm) at room temperature in the presence of 50 mg of platinum oxide. The theoretical amount of hydrogen was adsorbed in 3 h and the solution was basified with 6 M NaOH, extracted with three 50-mL portions of dichloromethane, and dried (K_2CO_3). Concentration afforded 165 mg of nearly pure **1** as a colorless oil. Purification was effected by treatment with HCl-saturated ether, concentration, and trituration with hexane to afford 170 mg (83% from **18**) of pure *dl*-pumiliotoxin C (**1**) hydrochloride, mp (sealed capillary) 232–234 °C. One recrystallization from 2-propanol or 1:3 ethanol–ethyl acetate afforded an analytical sample: mp 243–244 °C (sealed capillary); ν_{max} ($CHCl_3$, 0.02 M) 2500–3000, 1584, 1445, 1380, and 950 cm^{-1}; ^1H NMR ($CDCl_3$, D_2O, δ) 3.30 (m, half-height width = 9 Hz, C_{8a} H), 2.95 (m, half-height width = 20 Hz, C_2H), 0.92 (t, J = 6 Hz, CH_2CH_3), 0.88 (d, J = 6 Hz, CH_3CH); ^{13}C NMR ($CDCl_3$, δ) 60.1 (d, C_2), 58.1 (d, C_{8a}), 41.0 (d, C_{4a}), 35.0 (t, C_6),* 34.6 (t, $CH_2CH_2CH_3$),* 29.2 (t, C_8), 27.4 (d, C_5), 25.3 (t, C_3), 23.3 (t, C_4), 20.7, (t, C_7), 19.8 (q, CH_3CH), 18.9 (t, CH_2CH_3), 13.8 (q, CH_2CH_3) (an asterisk indicates that assignment may be reversed);[31] mass spectrum (free base) 195.200 (5%, $C_{13}H_{25}N$ requires 195.199), 152 (100%). Anal. ($C_{13}H_{26}ClN$) C, H, N.

Synthetic *dl*-**1** hydrochloride showed the same ^1H NMR, ^{13}C NMR, IR, and mass spectra as the hydrochloride of natural pumiliotoxin C, and was identical by mixture melting point and GLC analysis on two columns[36] with samples of racemic pumiliotoxin C hydrochloride, kindly provided by Professors Ibuka, Inubushi, and Habermehl, which were prepared by independent routes.

Preparation of *dl*-Pumiliotoxin C from Benzyl *trans*-1,3-Butadiene-1-carbamate (19). A. Diels–Alder Reaction of Diene 19 and *trans*-Crotonaldehyde. Preparation of Endo Adduct 20. A solution of **19**[15b,c] (20.3 g, 0.10 mol), 4-*tert*-butylcatechol (ca. 100 mg), and 100 mL of freshly distilled *trans*-crotonaldehyde was heated at 110 °C in a sealed glass ampule for 160 min. Concentration afforded a light yellow semisolid. Careful ^1H NMR analysis (see Table I) of a comparable sample showed that one cycloadduct (CHO δ 9.68) predominated to the extent of ca. 90%. Crystallization of the crude adduct from hexane–ethyl acetate gave 13.0 g (48%) of pure **20,** mp 73–74 °C. Chromatography of the concentrated filtrate on 300 g of silica gel (7:3 hexane–ethyl acetate) afforded an additional 5.3 g (19%) of crystalline, chromatographically pure **20,** together with 2.2 g of crystalline diene **19.** The total isolated yield of **20** was 18.3 g (67%), which represents a 76% yield based on nonrecovered diene. One recrystallization from hexane–ethyl acetate yielded an analytical specimen: mp 74–75 °C; ν_{max} (Nujol) 3300, 1700, 1530, and 1250 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 9.68 (d, J = 1.8 Hz, CHO), 7.4 (broad s, C_6H_5), 5.3–6.0 (m, C*H*=C*H*), 5.2–5.4 (m, NH), 5.09 (s, $CH_2C_6H_5$), 4.3–4.6 (m, C*H*NH), 1.07 (d, J = 6.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, δ) 203.1, 155.8, 136.5, 129.2, 128.5 (2 C), 128.0 (3 C), 125.8, 66.8, 56.2, 45.2, 31.4, 25.0, 19.2; mass spectrum 273.136 (0.4%, $C_{16}H_{19}NO_3$ requires 273.136), 182 (11%), 138 (15%), 94 (39%), 91 (100%). Anal. ($C_{16}H_{19}NO_3$) C, H, N.

B. Preparation of Dienone Carbamate 21. Following a procedure similar to that described for the preparation of **17,** 273 mg (1.00 mmol) of **20** was olefinated with dimethyl 2-oxopentylphosphonate[27] to give 406 mg of a crude semisolid material. Recrystallization from 4 mL of hexane–ether (ca. 20:1) afforded 226 mg (66%) of pure **21,** mp 74–75 °C. Chromatography of the concentrated filtrate on 20 g of silica gel (7:3 hexane–ethyl acetate) yielded an additional 48 mg of crystalline **21,** mp 72–75 °C. The total isolated yield of **21** was 274 mg (80%). Two recrystallizations from hexane–ether yielded an analytical specimen: mp 75–76 °C; ν_{max} (Nujol) 3300, 1710, 1690, 1600, and 1535 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 7.33 (broad s, C_6H_5), 6.68 (dd, J = 16 and 9.4 Hz, C*H*=CHCO), 6.14 (d, J = 16 Hz, =CHCO), 5.5–5.9 (m, C*H*=C*H*), 5.07 (s, $CH_2C_6H_5$), 4.6–4.7 (broad s, NH), 4.2–4.5 (m, C*H*NH); ^{13}C NMR ($CDCl_3$, δ) 200.4, 155.8, 136.6, 146.0, 132.5, 129.8, 128.6 (2 C), 128.2 (2 C), 128.1, 126.3, 66.8, 48.5, 48.3, 41.9, 32.4, 28.5, 19.8, 17.7, 13.8; mass spectrum 341.199 (0.4%, $C_{21}H_{27}NO_3$ requires 341.199), 203 (19%), 108 (26%), 91 (100%). Anal. ($C_{21}H_{27}NO_3$) C, H, N.

C. Conversion of 21 to *dl*-Pumiliotoxin C(1) Hydrochloride. A solution of **21** (170 mg, 0.50 mmol), 2.4 mL of 0.20 M HCl (0.48 mmol), and 50 mL of ethanol was treated overnight with hydrogen (1 atm) at room temperature in the presence of 25 mg of 10% palladium on carbon. The catalyst was removed by filtration through Celite, a drop of concentrated HCl was added, and the ethanol solution was concentrated to give a white solid residue. Recrystallization from 2-propanol afforded 110 mg (95%) of pure *dl*-pumiliotoxin C hydrochloride, mp 241–242 °C (sealed capillary). This material was identical by mixture melting point, ^1H NMR, and ^{13}C NMR with *dl*-pumiliotoxin C hydrochloride prepared from diene **9.**

D. ^1H NMR Investigation of the Cycloadducts Formed from the Reaction of Diene 19 and *trans*-Crotonaldehyde. We found the ^1H NMR of the aldehyde region (δ 9.5–10.0) to be useful for following the progress of the cycloaddition reaction. In addition to residual *trans*-crotonaldehyde (δ 9.49, d, J = 7.8 Hz), the following absorptions were clearly observable in 90-MHz spectra: a doublet at δ 9.68 (J = 1.8 Hz) for the endo adduct **20,** a doublet at δ 9.78 (J = 1.6 Hz) which is attributed to the epimer at the formyl-bearing carbon of adduct **20** (compare with adduct **11**), a doublet at δ 9.83 (J = 1.6 Hz) due to an unknown (exo?) adduct, and a doublet at δ 9.62 (J = 4.4 Hz) due to an unknown product, which is presumed not to be a cycloadduct on the basis of the large coupling constant. A semiquantitative study of the effect of temperature and reaction time on the product mixture resulting from the reaction of diene **19** and *trans*-crotonaldehyde was conducted in the following fashion. Aliquots (ca. 0.5 mL) of a 1.0 M stock solution of **19** in *trans*-crotonaldehyde were sealed in glass ampules, placed in a constant-temperature bath (±1 °C) for a given time, concentrated on a rotary evaporator (bath temperature <40 °C), and analyzed by ^1H NMR. The results are summarized in Table **I.**

Preparation of (2α,4aβ,5β,8aβ)-2,5-Dipropyldecahydroquinoline (23) Hydrochloride from Diene 19. A solution of diene **19** (3.1 g, 15 mmol) and 15 mL of freshly distilled *trans*-2-hexenal was heated at 110 °C in a sealed glass ampule for 180 min. Excess *trans*-2-hexenal was removed by distillation at 25 °C (<0.03 mm) and collected at −78 °C for reuse. ^1H and ^{13}C NMR analysis of the resulting yellow oil (4.3 g) indicated that cycloadduct **22** (CHO δ 9.62) was formed to the extent of greater than 80%. Attempted purification of a portion of this material (1.73 g) by chromatography on silica gel (hexane–ethyl acetate) resulted in the recovery of 290 mg of diene **19** and the isolation of the cycloadduct (840 mg, 50%) as a 1:1 mixture of isomers (presumably epimers at the formyl-bearing carbon): CHO δ 9.62 (J = 1.2 Hz) and 9.74 (J = 1.3). As a result the crude cycloadduct was used directly for the phosphonate olefination. The ^{13}C NMR spectrum ($CDCl_3$, δ) of the crude cycloadduct showed peaks for adduct **22** at 203.3, 155.8, 66.6, 53.6, 45.0, 35.0, 30.5, 27.9, 19.7, 13.8.

A 1.50-g portion of the crude cycloadduct was treated with the sodium salt of dimethyl 2-oxopentylphosphonate[27] (0.97 g, 5.0 mmol), following the procedure described for the preparation of **17**, to yield 2.4 g of a pale yellow oil. Purification by chromatography on 125 g of silica gel (89:10:1 hexane–ethyl acetate–triethylamine) yielded 300 mg of recovered diene **19** and 1.22 g (64% from diene **19**) of dienone carbamate **27** (ca. 90% pure by ^1H and ^{13}C NMR) which was used directly for the next step. A pure sample of **27** was obtained by preparative TLC (silica gel, 9:1 hexane–ethyl acetate, R_f 0.2–0.4): a colorless oil, mass spectrum m/e 369.[38]

A 920-mg portion of the sample of **27** described above was hydrogenated, following the procedure described for the preparation of **1** from **21**, to afford, after recrystallization from ethanol–ethyl acetate, 570 mg (56% from diene **19**) of pure **23** hydrochloride, mp 197–198 °C (sealed capillary). Two recrystallizations from ethanol–ethyl acetate yielded an analytical specimen: mp 198–199 °C (sealed capillary); ν_{max} ($CHCl_3$, 0.03 M) 2500–3000, 1590, 1460, 1450, and 1430 cm^{-1}; ^1H NMR ($CDCl_3$, D_2O, δ) 3.3 (m, half-height width = 10 Hz, C_{8a} H), 2.9 (m, half-height width = 22 Hz, C_2 H); ^{13}C NMR ($CDCl_3$, δ) 60.2 (C_2), 58.5 (C_{8a}), 39.1 (C_{4a}), 35.3, 34.6, 31.4 (2 C), 29.1, 25.2, 23.4, 20.7, 19.3, 18.9, 14.5, 13.8; mass spectrum (free base) 223 (5%), 181 (14%), 180 (100%). Anal. ($C_{15}H_{30}ClN$) C, H, N.

Preparation of Dimethyl 2-Oxo-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]heptylphosphonate (24). The method of Corey and Kwiatkowski was used.[27] A solution of *n*-butyllithium (50 mL of a 2.1 M hexane solution) and 100 mL of THF was cooled to −78 °C and treated dropwise with dimethyl methylphosphonate (12.4 g, 100 mmol). The resulting suspension was stirred at −78 °C for 30 min. A solution of ethyl 6-[(tetrahydro-2*H*-pyran-2-yl)oxy]hexanoate [37] (24.4 g, 100 mmol, prepared from 6-hexanolactone, in 50% overall yield, by sequential treatment with ethanol–H_2SO_4 and dihydropyran–*d*-camphorsulfonic acid) and 100 mL of THF was then added dropwise over 10 min, while the reaction temperature was maintained at −78 °C. The resulting mixture was stirred at −78 °C for 22 h, and then poured into 500 mL of brine. After careful neutralization with concentrated H_2SO_4, the mixture was extracted with five 100-mL portions of dichloromethane, and the combined extracts were dried (K_2CO_3) and concentrated to give 40 g of a yellow liquid. Chromatography on 400 g of silica gel (99:1 ethyl acetate–triethylamine) resulted in the isolation of 8.8 g (36%) of the starting hexanoate ester and 11.6 g (36%, 56% based on nonrecovered ester) of pure **24**: ^1H NMR (CCl_4, acetone-d_6, δ) 4.49 (broad s, OCHO), 3.1–4.0 (m, two CH_2O), 3.70 (d, J^3_{PH} = 11.1 Hz, CH_3O), 2.99 (d, J^2_{PH} = 22.7 Hz, CH_2PO), 2.59 (broadened t, J = 6.7 Hz, CH_2CO); ^{13}C NMR ($CDCl_3$, δ) 200.3 (J^2_{CP} = 6.1 Hz), 97.7, 75.7, 66.1, 52.9, 51.8 (J^2_{CP} = 6.1 Hz, 2 C), 40.1 (J^1_{CP} = 24.5 Hz), 29.8, 28.6, 24.7 (2 C), 22.2, 18.7.[39]

Preparation of (2α,4aβ,5β,8aβ)-2-(5-Hydroxypentyl)-5-methyldecahydroquinoline (25) from Endo Adduct 20. Aldehyde **20** (180 mg, 0.66 mmol) was treated with the sodium salt of **24** (220 mg, 0.68 mmol), following the procedure described for the preparation of **17**, to give a yellow oil. Purification by chromatography on 50 g of silica gel (4:1 hexane–ethyl acetate) afforded 260 mg (84%) of pure dienone carbamate **26**, a colorless oil which solidified in the freezer, mass spectrum 469.282 ($C_{28}H_{39}NO_5$ requires 469.283).

Dienone carbamate **26** (1.66 g, 3.53 mmol) was hydrogenated, following the procedure described for the preparation of **1** from **21**, to afford 1.06 g of a colorless oil. The tetrahydropyranyl protecting group was removed by treating this oil for 18 h at room temperature with 50 mL of methanol and 5 mg of *d*-camphorsulfonic acid. Concentration and chromatography of the residue on 100 g of silica gel (4:1:1 hexane–ethanol–ethyl acetate, containing 1% NH_4OH) afforded 646 mg (76%) of pure **25** as a white, crystalline solid. Two recrystallizations from hexane afforded an analytical specimen: mp 69–70 °C; ν_{max} (CCl_4, 0.04 M) 3630, 3100–3500 (broad, weak), 1450, 1370, and 1310 cm^{-1}; ^1H NMR ($CDCl_3$, δ) 3.63 broadened t, J = 6 Hz, CH_2OH), 2.80 (broad s, half-height width = 7 Hz, C_{8a} H), 2.50 (m, half-height width = 21 Hz, C_2 H), 0.84 (d, J = 6.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$, δ) 63.0 (CH_2OH), 58.0 (C_2), 56.1 (C_{8a}), 42.7 (C_{4a}), 37.6, 36.1, 33.6, 32.9, 27.6 (2 C), 27.2, 26.1, 25.9, 21.4, 20.0; mass spectrum m/e 240 (1%), 239 (1%), 196 (10%), 152 (100%). Anal. ($C_{15}H_{29}NO$) C, H, N.

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Supplementary Material Available: Spectroscopic data for enones **13, 16, 27,** and **26** (2 pages). Ordering information is given on any current masthead page.

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(20) A. Terada, *Nippon Kaguku Zasshi*, **81**, 1773 (1960); A. Terada and K. Murata, *Ibid.*, **83**, 490 (1962).
(21) (a) The use of 1-benzylamino-1,3-butadiene, formed in situ from 1,3-bis(benzylamino)-1-butene, as a 1-amino-1,3-butadiene synthetic equivalent has been described in the patent literature: G. Satzinger, private communication. (b) The preparation of *trans*-*N*-benzyl-*N*-acyl-1-amino-1,3-butadienes from crotonaldehyde has been recently accomplished: W. Oppolzer, private communication.
(22) W. S. Wadsworth, Jr., and W. D. Emmons, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 547.
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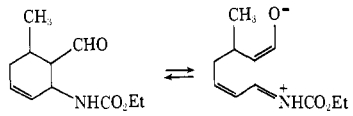
Oxford, 1969, Chapter 4-2.

(25) An alternate explanation, involving retro-Mannich scission of the cyclohexane ring (eq i), appears ruled out since such a process can lead to epimerization at both the methyl- and aldehyde-bearing ring carbons. The all-trans adduct **14** would be expected to result from such an epimerization mechanism.



(i)

(26) Unpublished observations of G. F. Taylor and P. J. Jessup.

(27) Prepared from ethyl butyrate by the method of Corey and Kwiatkowski: E. J. Corey and G. T. Kwiatkowski, *J. Am. Chem. Soc.*, **88**, 5653 (1966).

(28) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals", Academic Press, New York, N.Y., 1967, Chapter 25.

(29) The high endo stereoselectivity observed in the reaction of *trans*-crotonaldehyde with acylaminobutadienes **9** and **19** is surprising in light of the low endo stereoselectivity reported for the reaction of this dienophile with cyclopentadiene,[18] and the moderate endo stereoselectivity observed in the reaction of diene **9** and methyl acrylate.[19] Whether the acylaminobutadienes or cyclopentadiene is unusual in this regard is the object of current attention in our laboratory.

(30) H. Booth, D. V. Griffiths, and M. L. Jozefowicz, *J. Chem. Soc., Perkin Trans. 2*, 751 (1976); F. W. Vierhapper and E. L. Eliel, *J. Org. Chem.*, **42**, 51 (1977).

(31) A full analysis of the ^{13}C NMR spectra of 2,5-substituted *cis*-decahydroquinolines will be reported elsewhere.

(32) Tetrahydrofuran (THF) was distilled from benzophenone and sodium immediately prior to use, and 4-*tert*-butylcatechol was purified by sublimation and recrystallization from hexane. All reactions were conducted under a nitrogen atmosphere.[33] Concentrations were done using a rotary evaporator under reduced pressure. Commercial plates coated with E. Merck silica gel were used for thin layer chromatography (TLC). W. R. Grace silica gel (grade 62) was used for column chromatography. ^1H and ^{13}C NMR spectra were determined with a Bruker WH-90 spectrophotometer at 90 and 22.6 MHz, respectively. Chemical shifts are reported as δ values in parts per million relative to internal tetramethylsilane = 0. ^1H NMR coupling constants (J) are reported in hertz and refer to apparant multiplicities, and not true coupling constants; abbreviations used are s, singlet; d, doublet; t, triplet; m, complex multiplet. In a few cases these abbreviations are also used to refer to the peak multiplicities observed in off-resonance decoupled ^{13}C NMR spectra. Infrared spectra were determined with a Beckman Acculab 2 spectrometer. Mass spectra were determined at 75 eV with a Du Pont 21-492B double-focusing spectrometer at the Caltech analytical facility. High-performance liquid chromatography (HPLC) was performed with Waters components consisting of a 6000-A pump, U6K injector, and R401 differential refractometer. Gas chromatography (GLC) utilized a Varian Model 3700 chromatograph equipped with a differential thermal conductivity detector. Microanalyses were performed by Galbraith Laboratories, and agreed with calculated values within ±0.4%. Melting points were determined in capillary tubes with a Thomas-Hoover apparatus which was calibrated with known standards.

(33) W. S. Johnson and W. P. Schneider, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 132.

(34) A 30 cm × 4 mm μ Porasil column (ca. 3500 theoretical plates) and the eluent 9:1 hexane–ether were used for this analysis.

(35) A 12 ft × $\frac{3}{8}$ in. Porasil A column was used for this separation.

(36) (a) A 6 ft × $\frac{1}{8}$ in. 3% SP-2401 on 100/120 Supelcoport glass column, 100–140 °C, N_2. (b) A 6 ft × $\frac{1}{8}$ in. 10% Carbowax 20M–2% KOH on 80/100 Chromosorb W AW stainless steel column, 100–180 °C, N_2.

(37) G. Defaye, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **19**, 1 (1971); *Chem. Abstr.*, **75**, 36457s (1972).

(38) Spectroscopic data for this compound are reported in the microfilm edition of this article.

(39) NOTE ADDED IN PROOF. The use of 2.1 equiv. of the lithium salt of dimethyl methylphosphonate improves the yield of **24** to 78%.

Bimolecular Reactions of Pyridinyl Radicals in Water and the Mechanism of NAD+–NADH Dehydrogenase Reactions†

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Abstract: 1-Methyl-3-carbamido- (**3**·) and 4-carbamidopyridinyl (**4**·) radicals, generated through pulse radiolysis via 1e addition to the pyridinium ions, disappear by rather different pathways in water. **3**· dimerizes in a pH-independent reaction, whereas **4**· reacts by electron transfer with protonated **4**· (**4**H+·) and **4**H+· reacts with other **4**H+·, leading to a pH-dependent reaction yielding pyridinium ion and a dihydropyridine. The latter reaction was defined with respect to both kinetics and products by a study of the disappearnce of 1-ethyl- and 1-*tert*-butyl-4-carbomethoxypyridinyl in aqueous solutions between pH 8 and 9. At higher pH, ester hydrolysis produces the highly reactive carboxylate-substituted radical. A log k–pH plot suggests pK_a differences between ester and amide radicals. Dimerization and electron-transfer reactions of **2**·, **3**·, and **4**· pyridinyl radicals generated by radiolytic techniques can be distinguished by careful measurement of pH changes of unbuffered solutions. Both the **3**· dimer and the dihydropyridine from **4**· react with water in pH-dependent reactions to yield derivatives absorbing at much shorter wave lengths. The pK_a for **3**· is 1.4, but the structurally similar radical from nicotinamide adenine dinucleotide (NAD·) is unprotonated at pH 0.3. The NAD· dimer reacts with water at about 0.03 of the rate found for **3**· dimer. Some properties of the product of combination of the hydroxy-*tert*-butyl radical and **3**· are compared to those of the **3**· dimer. The suggested 1e, H+, pathway for NAD+–NADH enzyme-catalyzed reactions is made more attractive by our results.

Introduction

Two streams of thought underlie current interest in pyridinyl radicals (Py·). The first began with the work of Gomberg on the triphenylmethyl radical and proceeded through dissociable pyridinyl radical dimers,[2] dialkylbipyridylium dications and cation radicals[3,4] (viologen, Paraquat[5,6]), and stable, isolable pyridinyl radicals.[7] The second began with the discovery that two of the most important coenzymes in biological systems, NAD and NADP,[8] had pyridiunium rings as their active centers,[9] found stimulus in 1e reactions of dihydropyridines,[10] receded somewhat amidst the controversy involving 1e vs. 2e reductions,[11] regained strength through the pulse radiolytic

† The authors dedicate this paper to the memory of Gabriel Stein, late Professor at the Hebrew University, Jerusalem, who contributed so significantly to the field of the present paper and to other areas of radiation chemistry, through both his own work and his enthusiastic encouragement of others.

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